

EFNS guideline on the treatment of cerebral venous and sinus thrombosis in adult patients

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Background: Cerebral venous and sinus thrombosis (CVST) is a rather rare disease which accounts for < 1% of all strokes. Diagnosis is still frequently overlooked or delayed as a result of the wide spectrum of clinical symptoms and the often subacute or lingering onset. Current therapeutic measures which are used in clinical practice include the use of anticoagulants such as dose-adjusted intravenous heparin or body weight-adjusted subcutaneous low-molecular-weight heparin (LMWH), the use of thrombolysis and symptomatic therapy including control of seizures and elevated intracranial pressure.

Methods: We searched MEDLINE (National Library of Medicine), the Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Library to review the strength of evidence to support these interventions and the preparation of recommendations on the therapy of CVST based on the best available evidence. Review articles and book chapters were also included. Recommendations were reached by consensus. Where there was a lack of evidence but consensus was clear we stated our opinion as good practice points.

Results and conclusions: Patients with CVST without contraindications for anticoagulation (AC) should be treated either with body weight-adjusted subcutaneous LMWH or with dose-adjusted intravenous heparin (level B recommendation). Concomitant intracranial haemorrhage (ICH) related to CVST is not a contraindication for heparin therapy. The optimal duration of oral anticoagulant therapy after the acute phase is unclear. Oral AC may be given for 3 months if CVST was secondary to a transient risk factor, for 6–12 months in patients with idiopathic CVST and in those with “mild” thrombophilia, such as heterozygous factor V Leiden or prothrombin G20210A mutation and high plasma levels of factor VIII. Indefinite AC should be considered in patients with recurrent episodes of CVST and in those with one episode of CVST and ‘severe’ thrombophilia, such as antithrombin, protein C or protein S deficiency, homozygous factor V Leiden or prothrombin G20210A mutation, antiphospholipid antibodies and combined abnormalities (good practice point). There is insufficient evidence to support the use of either systemic or local thrombolysis in patients with CVST. If patients deteriorate despite adequate AC and other causes of deterioration have been ruled out, thrombolysis may be a therapeutic option in selected cases, possibly in those without large ICH and threatening herniation (good practice point). There are no controlled data about the risks and benefits of certain therapeutic measures to reduce an elevated intracranial pressure (with brain displacement) in patients with severe CVST. However, in severe cases with impending herniation craniectomy can be used as a life-saving intervention (good practice point).

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Background and objectives

Cerebral venous and sinus thrombosis (CVST) is a rare condition which accounts for < 1% of all strokes. The

exact incidence in adults is unknown because population-based studies are not available but one can expect 5–8 cases per year in a tertiary care centre [1,2]. A Canadian study reported an incidence of 0.67 cases per 100 000 children below 18 years, and 43% of the reported cases were seen in neonates [3]. The peak incidence in adults is in their third decade with a male/female ratio of 1.5–5 per year [2,4]. Diagnosis is still frequently overlooked or delayed because of the wide spectrum of clinical symptoms and the often subacute or lingering onset. Headache is the most frequent symptom of CVST and occurs in almost 90% of all cases [5]. The headache may be of acute onset (thunderclap headache) and may be clinically indistinguishable from headache in patients with subarachnoid haemorrhage [6]. Focal or generalized seizures are far more frequently seen in CVST than in arterial stroke and occur in 40% of all patients with an even higher incidence (76%) in peripartum CVST [5,7]. Focal neurological signs (including focal seizures) are the most common finding in CVST. They include central motor and sensory deficits, aphasia or haemianopsia and occur in 40–60% of all cases. In patients with focal deficits together with headache, seizures or an altered consciousness, CVST should always be considered. The syndrome of isolated intracranial hypertension (IIH) with headache, vomiting and blurred vision because of papilloedema is the most homogeneous pattern of clinical presentation accounting for 20–40% of CVST cases. Stupor or coma is found in 15–19% of patients at hospital admission [5,8] and is usually seen in cases with extensive thrombosis or affection of the deep venous system with bilateral thalamic involvement. Of all clinical signs reported in CVST, coma at admission is the most consistent and strongest predictor of a poor outcome [4,5].

Intra-arterial four-vessel angiography has long been the gold standard for establishing the diagnosis of CVST but today magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) are regarded the best tools both for the diagnosis and follow-up of CVST (for review see [9]). Cranial computed tomography (CCT) alone is not sufficient but diagnosis can be established in combination with CT angiography although the use of iodinated contrast fluid and ionizing radiation remains a disadvantage which makes it inappropriate for follow-up examinations.

Current therapeutic measures which are used in clinical practice include the use of anticoagulants such as dose-adjusted intravenous heparin or body weight-adjusted subcutaneous low-molecular-weight heparin (LMWH), the use of thrombolysis and symptomatic therapy including control of seizures and elevated intracranial pressure. Particularly, the use of heparin has long been a matter of debate. Whereas anticoagu-

lation (AC) is effective in the treatment and prevention of extracerebral venous thrombosis, the high rate of spontaneous intracranial haemorrhages (ICHs) seen in patients with CVST let many physicians hesitate to administer heparin because of safety concerns. The introduction of local thrombolysis has stirred the discussion about the optimal therapy of patients with CVST [10].

The aim of the present Task Force was to review the strength of evidence to support these interventions and the preparation of recommendations on the therapy of CVST based on the best available evidence for the efficacy and safety of anticoagulant therapy, thrombolysis and symptomatic therapy.

Materials and methods

Search strategy

MEDLINE 1966–2009 and EMBASE 1966–2009 were examined with appropriate MESH and free subject terms: 1. CVST, 2. cerebral venous thrombosis, 3. cortical vein thrombosis 4. intracranial thrombosis.

One to four was combined with the terms: 7. treatment, 8. medication, 9. therapy, 10. controlled clinical trial, 11. randomized controlled trial, 12. multicentre study, 13. Meta-analysis, 14. AC, 15. thrombolysis, 16. local thrombolysis, 17. antiepileptic therapy, 18. intracranial pressure, 19. steroids, 20. hyperventilation, 21. osmotic diuretics, 22. craniectomy, 23. decompressive surgery.

The Cochrane Central Register of Controlled Trials and the Cochrane Library and references of selected articles were also searched. Review articles and book chapters were also included if they were considered to provide comprehensive reviews of the topic. The search included reports of research in human beings only and in English language. The Task Force included six neurologists and one specialist in Internal Medicine with an expertise in the field of haemostasis and thrombosis (I. M.). The literature search was performed by K.E. and F.M. who also prepared a first draft of the manuscript. The manuscript was sent via e-mail and was reviewed by all members of the Task Force, and suggestions and corrections were incorporated. Recommendations were reached by consensus of all Task Force members and were also based on our own awareness and clinical experience. Where there was a lack of evidence but consensus was clear we stated our opinion as good practice points. The final draft of the manuscript was approved by all members of the Task Force. All necessary steps for the preparation of the presented recommendation were performed via e-mail correspondence.

The classification for evidence levels for therapeutic interventions was made according to the guidance for

the preparation of neurological management guidelines by EFNS scientific task forces [11].

Treatment

Heparin therapy

The rationale of anticoagulant therapy in CVST is to avoid thrombus extension, to favour spontaneous thrombus resolution and to prevent pulmonary embolism particularly in patients with concomitant extracranial deep vein thrombosis. At the same time, AC may promote or worsen ICH which occurs in 40–50% of patients with CVST [5,12] and which may be the main reason to withhold AC. In addition, AC is always associated with an increased risk for extracranial bleeding complications.

There are only two small controlled trials which compared the efficacy and safety of AC with placebo for the treatment of CVST. Both trials chose an unfavourable outcome as the main criterion to evaluate the efficacy of AC instead of a good outcome (e.g. Rankin Scale 0–1) which might have been a better choice in a condition with a much better prognosis than arterial stroke. In addition, the 3-month follow-up for the evaluation of the functional outcome may have been too short because major improvement of the patients with CVST can be observed far beyond.

The first study [13] compared dose-adjusted intravenous heparin with placebo in 20 patients (10 patients in each treatment group) (class II evidence). Eight patients in the heparin group recovered completely and none died, whereas only one patient in the placebo group recovered fully and three patients died. Treatment assessment was performed using a specially developed CVST severity scale which contained the items headache, focal signs, seizures and level of consciousness. Using this scale, there was a significant difference between the two groups after 3 days in favour of the active treatment and the difference remained significant after 3 months. Three patients with previous ICH recovered completely, and no new haemorrhages occurred in the heparin group whereas in the placebo group, two patients with pre-treatment ICH died and two new haemorrhages were observed. There were no major extracranial haemorrhages in the heparin group and one probable case of fatal pulmonary embolism in the control group.

The outcome assessment was criticized [14] because the CVST severity scale was not validated as a final outcome measure in neurological patients. Using death and dependency as clearly defined outcome parameters, the difference between the two groups would not be significant. Nevertheless, the study did show some benefit and even more importantly suggested the safety of AC in patients with CVST.

The second randomized trial compared body weight-adjusted subcutaneous LMWH with placebo in 60 patients with CVST [12] (class I evidence). A poor outcome – defined as death or Barthel index < 15 – was observed after 3 weeks in six of the 30 patients treated with LMWH (20%) compared to seven of the 29 controls (24%). After 3 months, three patients (10%) in the LMWH group and six patients (21%) in the placebo group had a poor outcome which corresponded to a non-significant absolute risk reduction of 11% in favour of the active treatment. No new ICH or secondary worsening of the 15 patients with pre-treatment haemorrhage was observed in the LMWH group. There was one major extracerebral haemorrhage in the heparin group and one probable case of fatal pulmonary embolism in the control group.

A meta-analysis of these two trials showed that the use of AC led to an absolute risk reduction in death or dependency of 13% (confidence interval –30 to + 3%) with a relative risk reduction of 54% [15]. Although this difference did not reach statistical significance, both trials showed a consistent and clinically meaningful trend in favour of AC and demonstrated the safety of anticoagulant therapy. Thus, data from controlled trials favour the use of AC in patients with CVST because it may reduce the risk of a fatal outcome and severe disability and does not promote ICH at least in the small number of patients in the trials. In patients with ICH (and proven CVST) and threatened vision with the need for repeated lumbar punctures to remove cerebrospinal fluid (CSF) to obtain a normal closing pressure, AC should be withheld until 24 h after the last lumbar puncture.

It is unclear whether treatment with full-dose intravenous heparin or subcutaneously applied LMWH is equally effective for CVST. A meta-analysis which compared the efficacy of fixed-dose subcutaneous LMWH versus adjusted-dose unfractionated heparin for extracerebral venous thromboembolism found a superiority for LMWH and significantly less major bleeding complications [16]. Further advantages include the route of administration which increases the mobility of patients and the lack of laboratory monitoring and subsequent dose adjustments. A possible advantage of dose-adjusted intravenous heparin therapy particularly in critical ill patients may be the fact that the activated partial thromboplastin time normalizes within 1–2 h after discontinuation of the infusion if complications occur or surgical intervention is necessary.

Recommendation

Current evidence shows that patients with CVST without contraindications for AC should be treated

either with body weight-adjusted subcutaneous LMWH or with dose-adjusted intravenous heparin with an at least doubled activated partial thromboplastin time (level B recommendation). Concomitant ICH related to CVST is not a contraindication for heparin therapy. For the reasons mentioned elsewhere, LMWH should be preferred in uncomplicated CVST cases.

Thrombolysis

There is currently no evidence from randomized controlled trials about the efficacy and safety of either systemic or local thrombolytic therapy in patients with CVST. Thrombolytic therapy has the potential to provide faster restitution of venous outflow, and positive effects of local thrombolytic treatment of CVST have increasingly been reported from uncontrolled series [17–20] (class IV evidence). Patients were either treated with heparin and urokinase or treated with heparin and recombinant tissue plasminogen activator (rtPA) which may carry less bleeding complications owing to its clot selectiveness and shorter half-life. Two uncontrolled studies which used rtPA in combination with dose-adjusted intravenous heparin included a total of 21 patients [18,19]. In the Korean study [18] which included nine patients, a mean total dose of 135 mg (range 50–300 mg) rtPA was used compared to 46 mg (range 23–128 mg) in the American study [19] which included 12 patients. Both studies placed a microcatheter directly into the thrombus via the transfemoral vein and performed a bolus injection of rtPA followed by continuous infusion. In the two studies, combined, rapid (mean time of 20 h in the Korean and 29 h in the American study) and complete recanalization was achieved in 15 of 21 patients and 14 of 21 patients showed a complete clinical recovery. However, there were two extracerebral bleeding complications in the Korean study, and two patients with pre-treatment ICH in the American study worsened because of increased intracerebral bleeding which required surgery in one case. Thus, although recanalization was rapidly achieved, local thrombolysis may carry a higher risk of bleeding complications compared to anticoagulant therapy, particularly if pre-treatment ICH is present [10]. Trials that compare heparin therapy and local thrombolysis are lacking, and there is no evidence that clinical outcome is better than with heparin alone. Currently, local thrombolysis may be a therapeutic option for patients at high risk for a poor outcome despite heparin therapy. The International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) identified coma on admission and thrombosis of the deep venous system apart

from underlying causes as the most important predictors for a poor clinical outcome [5]. More than 80% of the included 624 adult patients were treated with AC. Comatose patients may define a subgroup of patients with CVST who are at high risk of death despite AC [8]. Under this particular condition, the effect of AC may come too late to prevent irreversible brain damage and these patients may possibly benefit from thrombolytic therapy. A systematic review on the use of thrombolytics in CVST suggested a possible benefit in such severe cases [21]. Thirty-eight of the reported patients were comatose at the start of thrombolytic therapy, of whom 6 (16%) died. ICH occurred in 17% and was associated with clinical deterioration in 5% of cases. In comparison, a retrospective analysis found that eight (53%) of the 15 patients with stupor or coma at the start of dose-adjusted intravenous heparin therapy died [8]. In the ISCVT, 12 (38%) of the 31 comatose patients died [5]. However, the results of the review were based on case reports and uncontrolled case series, and there are yet no established clinical criteria for the use of thrombolytics in CVST (class IV evidence). In a recent prospective study [22] of 20 patients treated with endovascular thrombolysis alone or in combination with endovascular thrombectomy (15 patients), 12 patients recovered, two survived with handicaps and six (30%) died. Twelve were comatose, and 14 had haemorrhagic infarcts before thrombolysis. Large haemorrhagic infarcts before treatment were associated with a fatal outcome, and five patients had increased ICH after thrombolysis. Patients with large infarcts and impending herniation did not benefit (class IV evidence).

A controlled randomized trial is warranted to further study the efficacy and safety of thrombolysis in CVST. However, such a trial will be difficult to perform in single centres because of the small number of severe patients, particularly in countries and centres with early diagnosis of CVST. Only an international multicentre trial may be able to clarify the role of thrombolysis in the treatment of CVST.

Recommendation

There is insufficient evidence to support the use of either systemic or local thrombolysis in patients with CVST. If patients deteriorate despite adequate AC and other causes of deterioration have been ruled out, thrombolysis may be a therapeutic option in selected cases, possibly in those without ICH or impending herniation from large haemorrhagic infarcts (good practice point). The optimal substance, dosage, route (systemic or local) or method of administration (repeated bolus or bolus plus infusion) are not known.

Oral anticoagulation

Controlled data about the benefit and optimal duration of oral anticoagulant therapy (OAT) in patients with CVST are not available, but most authors recommend continued AC after the acute phase. In the ISCVT, median time on OAT after discharge was 7.7 months [5]. A MRI follow-up study of 33 patients suggested that recanalization occurs within the first 4 months after CVST irrespective of further OAT [23]. These data may provide some guidance on the duration of OAT but whether incomplete or absent recanalization increases the risk of recurrence is not known (class IV evidence). No recurrences occurred in two follow-up studies which showed incomplete or no recanalization in more than 40% of the patients [23,24].

Analogous to patients with extracerebral venous thrombosis, OAT with a target international normalized ratio of 2.0–3.0 may be given for 3 months if CVST was secondary to a transient (reversible) risk factor and for 6–12 months if it was idiopathic [25]. However, the risk of recurrence of CVST may be lower than that of extracerebral venous thrombosis. In the ISCVT, 2.2% of all patients had a recurrent sinus thrombosis with a median follow-up of 16 months [5], and prolonged OAT may expose some patients to an unnecessary bleeding risk although there was also a risk of 4.3% for other thrombotic events during follow-up including 2.5% of pelvic or limb venous thrombosis and 0.5% of pulmonary embolism.

Oral anticoagulant therapy is also recommended for 6–12 months in patients with extracerebral venous thrombosis and ‘mild’ thrombophilia (heterozygous factor V Leiden or prothrombin G20210A mutation and high plasma levels of factor VIII) [26]. Long-term treatment should be considered for patients with ‘severe’ thrombophilia associated with a high risk of recurrence (antithrombin, protein C or protein S deficiency, homozygous factor V Leiden or prothrombin G20210A mutation, antiphospholipid antibodies and combined abnormalities) [26]. Indefinite OAT is also recommended in patients with two or more episodes of idiopathic objectively documented extracerebral venous thrombosis [25]. Thus, in the absence of controlled data, the decision on the duration of anticoagulant therapy must be based on individual hereditary and precipitating factors as well as on the potential bleeding risks of long-term OAT. Regular follow-up visits should be performed after discontinuation of OAT, and patients should be informed about early signs (headache) indicating a possible relapse.

Recommendation

There are insufficient data about the optimal duration of OAT in patients with CVST. Analogous to patients with a

first episode of extracerebral venous thrombosis, OAT may be given for 3 months if CVST was secondary to a transient risk factor, for 6–12 months in patients with idiopathic CVST and in those with ‘mild’ thrombophilia. Indefinite OAT should be considered in patients with two or more episodes of CVST and in those with one episode of CVST and ‘severe’ thrombophilia (good practice point).

Symptomatic treatment

Symptomatic therapy includes the use of antiepileptic drugs (AED), management of increased intracranial pressure, the control of psychomotor agitation and analgesic treatment.

Control of seizures

There are no data regarding the effectiveness of a prophylactic use of AED in patients with CVST. Whereas some authors recommend prophylactic treatment [27] because of the high incidence of seizures (and series of seizures or even status epilepticus) and their possible detrimental effects on the metabolic situation during the acute phase of the disease, others restrict the use of anticonvulsants to patients with seizures [28]. One study identified focal sensory deficits and the presence of focal oedema or ischaemic/haemorrhagic infarcts on admission CCT/MRI as significant predictors of early symptomatic seizures [29]. Another study [30] identified cortical vein thrombosis, ICH and focal motor deficits as independent predictors for early epileptic seizures (class IV evidence). Patients with supratentorial lesions and presenting seizures had the highest risk for recurrent seizures in the ISCVT which was significantly decreased by AED use [31] (class III evidence).

Although data are insufficient to give recommendations, these findings suggest that prophylactic treatment with AED may be a therapeutic option for those patients whereas it is not warranted when there are no focal neurological deficits and no supratentorial lesions on brain scan (e.g. patients with IIIH). If no antiepileptic treatment has been performed before the first seizure occurs, effective concentrations of AEDs should be achieved rapidly because series of seizures frequently occur in patients with CVST.

The risk of residual epilepsy after CVST is low compared to the high rate of patients with early seizures. Reported incidences range from 5% to 10.6% [5,29,32]. In the Portuguese series [29], all late seizures occurred within the first year. A haemorrhagic lesion in the acute brain scan was the strongest predictor of post-acute seizures. In all series together, late seizures were more common in patients with early symptomatic seizures than in those

patients with none. Thus, prolonged treatment with AED for 1 year may be reasonable for patients with early seizures and haemorrhagic lesions on admission brain scan, whereas in patients without these risk factors, AED therapy may be tapered off gradually after the acute stage.

Recommendation

Prophylactic antiepileptic therapy may be a therapeutic option in patients with focal neurological deficits and supratentorial lesions on admission CT/MRI (good practice point). The optimal duration of treatment for patients with seizures is unclear.

Treatment of elevated intracranial pressure

Although brain swelling is observed in about 50% of all patients with CVST on CCT, minor brain oedema needs no other treatment than AC which improves the venous outflow sufficiently to reduce intracranial pressure in most patients [27,28]. In patients with IIH and threatened vision, a lumbar puncture with sufficient CSF removal to obtain a normal closing pressure should be performed before starting AC 24 h after the puncture. There are no controlled data but acetazolamide may be considered in patients with persistent papilloedema. In few patients, vision continues to deteriorate despite repeated lumbar punctures and/or acetazolamide. In these cases, shunting procedures (lumboperitoneal, ventriculoperitoneal shunts or optic nerve fenestration) should be considered.

Antioedema treatment is necessary in only 20% of patients and should be carried out according to general principles of therapy of raised intracranial pressure (head elevation at about 30°, hyperventilation with a target PaCO₂ pressure of 30–35 mmHg, intravenous application of osmotic diuretics). However, one should keep in mind that osmotic substances might be harmful in venous outflow obstruction, as they are not as quickly eliminated from the intracerebral circulation as in other conditions. The use of tris-hydroxy-methyl-amino-methane (THAM) which decreases intracranial pressure (ICP) after intravenous administration via an alkalotic vasoconstriction may be a therapy option in ventilated patients. Restricted volume intake for treatment of brain oedema must be avoided, because these measures can cause an additional deterioration of blood viscosity. Steroids cannot be recommended for treatment of elevated intracranial pressure. No benefit was found in a case-control study of the ISCVT [33], and the use of steroids was associated with a detrimental effect in patients without parenchymal lesions (class III evidence).

The most frequent cause of death in patients with CVST is transtentorial brain herniation [34]. In severe

cases with impending herniation because of an unilateral large haemorrhagic infarct, decompressive surgery may be the only way to save the patient's life. Local thrombolysis seems no treatment option in such cases because of the incalculable risk of further ICH extension with an additional detrimental effect on ICP. Stefini and co-workers [35] reported three patients with fixed dilated pupils because of transtentorial herniation who underwent decompressive surgery two of whom recovered with only minor neurological sequelae (class IV evidence). Coutinho and co-workers [36] reported three consecutive cases treated with decompressive hemicraniectomy of whom two patients had an excellent outcome and one died. Reviewing the literature, the authors found another seven cases of severe CVST treated with decompressive surgery of whom all survived with a favourable outcome (modified Rankin scale ≤ 3) (class IV evidence). The haemorrhagic infarct should not be removed because neuronal damage is often less pronounced in CVST-related haemorrhage explaining the possible reversibility of even severe clinical symptoms [37].

Recommendations

In patients with IIH and threatened vision possible therapeutic measures may include one or more lumbar punctures, acetazolamide and incidentally CSF-shunting procedures. There are no controlled data about the risks and benefits of certain therapeutic measures to reduce an elevated intracranial pressure in patients with CVST. However, based on the available evidence, steroids seem not to be useful and should be avoided (good practice point). Antioedema treatment should be carried out according to general principles of therapy of raised intracranial pressure. In a small subgroup of patients with severe CVST and impending herniation attributable to large haemorrhagic infarcts, decompressive craniectomy can be life-saving (good practice point).

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