Epidemiology, diagnosis and treatment of cerebral venous thrombosis
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Anticoagulation for cerebral venous sinus thrombosis

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Abstract

Background
Treatment of cerebral venous sinus thrombosis with anticoagulants has been controversial. Anticoagulants may prevent new venous infarcts, neurologic deterioration and pulmonary embolism but may also promote hemorrhages.

Objectives
To assess the effectiveness and safety of anticoagulant therapy in patients with confirmed cerebral venous sinus thrombosis.

Search methods
We searched the Cochrane Stroke Group Trials Register (last searched August 2010), MEDLINE (1950 to August 2010), EMBASE (1980 to August 2010) and the Cochrane Central Register of Controlled Trials (The Cochrane Library, 2011 Issue 1). In an effort to identify further published, unpublished and ongoing trials we searched ongoing trials registers and reference lists of relevant articles, and contacted authors.

Selection criteria
Unconfounded randomized controlled trials in which anticoagulant therapy was compared with placebo or open control in patients with cerebral venous sinus thrombosis (confirmed by intra-arterial contrast, or venography with magnetic resonance, or venography with computed tomography imaging).

Data collection and analysis
Two review authors independently extracted outcomes for each of the two treatment groups (anticoagulant treatment and control). The outcome data for each patient were analyzed in the treatment group to which the patient was originally allocated (intention-to-treat analysis). We calculated a weighted estimate of the treatment effects across trials (relative risk, absolute risk reduction).

Main results
We included two small trials involving 79 patients. One trial (20 patients) examined the efficacy of intravenous, adjusted dose unfractionated heparin. The other trial
(59 patients) examined high dose, body weight adjusted, subcutaneous, low-molecular weight heparin (nadroparin). Anticoagulant therapy was associated with a pooled relative risk of death of 0.33 (95% confidence interval (CI) 0.08 to 1.21) and of death or dependency of 0.46 (95% CI 0.16 to 1.31). The absolute reduction in the risk of death or dependency was 13% (95% CI 30% to -3%). No new symptomatic intracerebral hemorrhages were observed. One major gastrointestinal hemorrhage occurred after anticoagulant treatment. Two control patients (placebo) had a diagnosis of probable pulmonary embolism (one fatal).

Authors’ conclusions
Based upon the limited evidence available, anticoagulant treatment for cerebral venous sinus thrombosis appeared to be safe and was associated with a potentially important reduction in the risk of death or dependency which did not reach statistical significance.
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Background

Cerebral venous sinus thrombosis (CVT) is a rare condition, with a highly variable clinical presentation and prognosis. The estimated incidence is about 2 to 4 per million people per year. A study in children less than 18 years old found a higher incidence of 6.7 per million per year (deVeber 2001). Symptoms and signs include headache, focal or generalized seizures, and neurologic deficits or coma (Bousser 2007; Stam 2005). Intracranial pressure is often elevated due to a diminished absorption of cerebrospinal fluid. This may cause papilledema and, rarely, visual impairment. Obstruction of the venous drainage may cause local cerebral edema and venous infarcts, which occur in approximately half of all patients (Ferro 2004). Venous infarcts are often hemorrhagic and may transform into large and possibly lethal cerebral hemorrhages. On the other hand, many patients have a benign course, with mainly signs of increased intracranial pressure but without neurologic impairment.

Treatment of CVT with anticoagulants has been controversial. Anticoagulant drugs are expected to arrest the thrombotic process and may prevent thrombus propagation, new venous infarcts and neurologic deterioration in patients with CVT. In addition, anticoagulants may prevent pulmonary embolism that can occur in these patients (Diaz 1992). Anticoagulation may also promote intracerebral hemorrhages (ICH), by causing hemorrhagic transformation of venous infarcts, although well-documented cases of such events are rare (Bousser 1997). In addition, anticoagulants always carry a risk of extracerebral hemorrhage (van Dongen 2004).

Several uncontrolled case series suggested that the neurological outcome after cerebral venous sinus thrombosis could be improved with heparin therapy, without an increase in hemorrhagic complications (Ameri 1992; Bousser 1985; Ferro 2001; Villringer 1994). One report described neurologic deterioration after anticoagulant treatment for sinus thrombosis in two patients (Gettefinger 1977), but these examples have been criticized: one patient received urokinase in addition to heparin, and the other developed CVT while on prophylactic subcutaneous heparin (Bousser 1997). In a large case series from Portugal, new intracranial hemorrhages developed in four of the 112 (3.6%) patients treated with anticoagulants, and in two of 30 (6.7%) patients who did not
receive anticoagulants (Ferro 2001). Einhaupl 1991 reported three new ICHs in an uncontrolled series of 56 patients (5.4%) treated with dose-adjusted intravenous heparin. Nevertheless, both studies reported that outcome was better for patients treated with anticoagulants.

In the early 1990s the first small randomized trials were set up to resolve the abovementioned therapeutic dilemma. This Cochrane Review aimed to combine the results of all randomized trials that compared anticoagulant treatment for CVT with control treatment without anticoagulants and that met pre-defined criteria.

**Objectives**

To review the best available evidence regarding the efficacy and safety of anticoagulant therapy in patients with CVT. We tested the following hypotheses among patients with confirmed CVT (thrombosis of at least one intracranial venous sinus or cerebral vein).

1. Treatment with therapeutic doses of unfractionated heparin, low-molecular-weight heparin, or coumarin(s) is associated with a reduced risk of being dead or dependent a few months after the onset of CVT.
2. Treatment with therapeutic doses of unfractionated heparin, low-molecular-weight heparin, or coumarin(s) is not associated with an increase in symptomatic intracranial or severe extracranial hemorrhages that may offset a treatment benefit.

**Methods**

**Types of studies**

We included all unconfounded randomized trials in which anticoagulant therapy was compared with placebo or open control in patients with confirmed CVT. In addition, we included studies that compared different anticoagulant regimens. We also sought open trials and non-blinded trials. If we found such trials, we planned to do sensitivity analyses, first including and then excluding them, to
determine the effect on the results. We excluded trials in which allocation to treatment or control group was not truly random or where allocation was not adequately concealed.

**Types of participants**
We selected trials that included patients with thrombosis of one or more intracranial venous sinuses documented by magnetic resonance imaging (MRI), computed tomography (CT) venography, or conventional angiography. We included trials that included patients with CVT and intracranial hemorrhage documented prior to anticoagulant treatment. We excluded trials that included patients diagnosed by CT scan alone, without CT-venography.

**Types of interventions**
We included all randomized controlled trials that compared the effects of anticoagulant therapy with placebo or open control on neurological outcome and death in patients with CVT. This included all anticoagulant regimens that aimed at a therapeutic level of anticoagulation, such as parenteral therapy with unfractionated heparin, low-molecular-weight heparin, heparinoids, or oral therapy with coumarin(s), or combinations, for at least three days. We also included studies which compared different types of heparin. We excluded trials which tested low-dose prophylactic anticoagulant regimens, antiplatelet agents, thrombolytic therapy, or defibrinogenating agents.

**Types of outcome measures**
We extracted the following outcomes of interest for each treatment group.

*Primary outcome measures*

1. Death from any cause at the end of the scheduled trial follow-up.
2. Death or dependency (needing help with activities of daily living) at the end of the scheduled trial follow-up.

*Secondary outcome measures*

1. Pulmonary embolism (diagnosed during life or at autopsy) within the scheduled treatment or follow-up period.
2. Symptomatic fatal or non-fatal intracranial hemorrhage, defined as any new intracranial hemorrhage or hemorrhagic transformation of a cerebral infarct that developed after randomization, that was documented by CT or MRI scanning, or at autopsy, and that caused clinically manifest neurologic deterioration.

3. Major extracranial hemorrhage, defined as any bleeding that required transfusion or significant surgical intervention, or that caused permanent disabling deficit (e.g. intra-ocular bleeding causing blindness).

Search methods for identification of studies
See the ‘Specialized register’ section in the Cochrane Stroke Group module. We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor on 6 August 2010. In addition, we searched MEDLINE (1950 to August 2010) (Appendix 1), EMBASE (1980 to August 2010) (Appendix 2) and the Cochrane Central Register of Controlled Trials (The Cochrane Library 2011, Issue 1) (Appendix 3). We developed the search strategies in collaboration with the Cochrane Stroke Group Trials Search coordinator. In an effort to identify further published, unpublished and ongoing trials we:

1. searched the following clinical trials registers (August 2010):
   i) ClinicalTrials.gov (www.clinicaltrials.gov);
   ii) Stroke Trials Registry (www.strokecenter.org/trials/);
   iii) WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/search/en/);

2. searched the bibliographies of all references chosen for full manuscript review;

3. Contacted authors who have published review articles, books, large case series or clinical trials in this topic.

We searched for trials in all languages and arranged translation of relevant articles published in languages other than English and Dutch.

Data collection and analysis
The review authors reviewed all titles obtained by the method outlined above. We discarded references obviously not relevant to the review question (primary
study population not CVT, case reports, and small descriptive case series). Two review authors (SFTM de B, JS) independently reviewed the abstracts of the remaining studies to establish whether they met the minimum selection criteria. We included abstracts classified by both review authors as ‘accepted’, or ‘unsure’ for further review. Abstracts rated by only one reviewer as either ‘accepted’, or ‘unsure’ were reviewed a second time by both and discrepancies resolved by discussion. Both review authors independently evaluated the full articles of the remaining references. Each review author rated each study as ‘accepted’, ‘unsure’ or ‘rejected’ based on the selection criteria. Where insufficient information was available, we tried to approach the authors for additional information.

For articles accepted into the review, two reviewers (SFTM de B, JS) independently extracted outcomes for each of the two treatment groups (anticoagulant treatment and control). We included the outcome data for each patient in the treatment group to which the patient was originally allocated (intention-to-treat analysis). We calculated a weighted estimate of the treatment effects across trials (relative risk, absolute risk reduction) using RevMan 5.0 (RevMan 2008).

Results

Description of studies
We identified a total of nine possibly relevant studies in the Cochrane Stroke Group Trials Register, 1717 references from the searches of MEDLINE and EMBASE and 103 references from the search of the Cochrane Central Register of Controlled Trials. From the results of these searches, we identified five potentially relevant studies (CVT Group 1999; Einhaupl 1991; Maiti 1997; Modi 2006; Nagaraja 1995). Four studies compared efficacy of heparin with control treatment (CVT Group 1999; Einhaupl 1991; Maiti 1997; Nagaraja 1995) and one study compared unfractionated heparin with low-molecular-weight heparin (Modi 2006). We did not find any studies that included pediatric patients and we did not identify any ongoing studies in the clinical trial registries.

Trials fulfilling the inclusion criteria
Einhaupl 1991 performed the first clinical trial of heparin in adult CVT patients. Sixty patients were planned to be included in a single centre trial (Germany),
which was stopped after the inclusion of 20 patients (planned interim analysis).
The diagnosis of CVT was made by intra-arterial contrast angiography. Patients with the usual contraindications for heparin were excluded. Treatment consisted of intravenous high-dose unfractionated heparin, 25,000 to 65,000 IU/day, after a bolus of 3000 IU, or placebo (saline infusion). The heparin dose was adjusted to obtain a partial thromboplastin time (PTT) value of at least twice the pretreatment value, and maximally 120 seconds. The treating physician was not blinded but the patients and the physicians who assessed the outcomes were. The primary outcome was the clinical condition at three months after randomization, assessed with a composite CVT severity scale, with items for headache, focal signs, seizures, and level of consciousness. Intracranial hemorrhage (ICH), diagnosed by one of two routine CT scans, was the secondary endpoint. After 10 patients in each treatment group were included the study was stopped because a statistically significant effect in favor of heparin was found, based upon scores on the CVT severity scale. Patients in both treatment groups were balanced for baseline variables, except with regard to the duration from onset of symptoms to the start of treatment, which was 33 days in the heparin group and 25 days in the placebo group.

In the placebo group, three patients died, six survived with a minor deficit and one recovered completely. In the heparin group, two patients had minor deficits and eight recovered completely. According to the CVT severity scale patients with a minor deficit may have slight to severe headaches, transient to mild paresis, or seizures. For the meta-analysis we considered all surviving patients with a minor deficit at three months as good outcomes (independent). There were two patients with new ICHs in the control group, and none in the heparin group. It is not clear whether these ICHs were symptomatic or only detected on the follow-up CT scans.

CVT Group 1999 included 60 adult patients in a multicentre trial in the Netherlands and in the UK. The diagnosis of CVT was made by intra-arterial contrast angiography or by MRI and MR angiography. Patients with the usual contraindications, including recent lumbar puncture for heparin, were excluded. Treatment consisted of subcutaneous low-molecular- weight heparin (nadroparin) in a dose of 180 anti-factor Xa U/ kg/24 hour or placebo, administered by two subcutaneous injections daily for three weeks. Patients,
treating physicians, and assessors were blinded during the first three weeks. Patients allocated to nadroparin received follow-up treatment with warfarin (non-blinded) for 10 weeks (total duration of anticoagulant treatment 13 weeks). Primary outcomes were scores on the Barthel index (activities of daily living), and on a stroke handicap scale (The Oxford handicap scale), and death. Secondary endpoints were symptomatic ICH and severe extracranial hemorrhage. Assessments were done at three weeks (blind), and at 12 weeks (non-blinded). Sixty patients were randomized (30 in each treatment group). Patients in both treatment groups were balanced for baseline variables, except for isolated intracranial hypertension and CT/MRI infarcts (see below). One patient from the placebo group was withdrawn after randomization (wrong diagnosis: arterial cerebral infarction). He was independent after three and 12 weeks.

After 12 weeks four of the 30 participants (13%) in the nadroparin group had a poor outcome, defined as death or dependence (Oxford handicap score 3 to 5). In the placebo group six of the 29 participants (21%) had a poor outcome. The open assessment showed essentially similar results to the blind assessment and is used in our meta-analysis. There were no symptomatic intracranial hemorrhagic complications. One patient in the nadroparin group had a major non-fatal gastrointestinal hemorrhage.

Excluded studies
A study from India randomized 57 women with puerperal CVT (Nagaraja 1995). We excluded this study because the diagnosis was not confirmed by our pre-defined criteria (angiography, MRI/ MRA or CT-venography) but by CT only. Patients with signs of cerebral hemorrhage on CT were excluded. Patients were initially treated with intravenous unfractionated heparin, 5000 IU every six hours, and then dose-adjusted to reach a PTT of 1.5 times the initial value. Details of the randomization procedure, allocation concealment, and pre-defined outcome measures were not given in the published article. Assessment was non-blinded. Twenty-nine patients received heparin and 28 were controls. Two patients in the control group died, and one had a residual paresis at six months. In the heparin group all patients recovered.

A second study from India reported a randomized controlled trial of 40 patients (20 heparin, 20 placebo). This study has been published as an abstract only
(Maiti 1997). According to the abstract, mortality was 15% in the heparin group and 40% in the placebo group. Details of diagnostic confirmation, the randomization procedure, allocation concealment, and pre-defined outcome measures have not been published. In a personal communication, however, the lead author reported that CVT was not diagnosed by angiography, MRI/MRA or CT-venography in all patients. No placebo was given to the control group and the physicians were not blinded to the treatment allocation. Because of these methodological limitations and the fact that the full results have not been published in a peer-reviewed journal, we excluded the study from the analysis.

Studies awaiting classification
We also identified a single randomized controlled trial which compares unfractionated heparin with low-molecular-weight heparin in CVT (Modi 2006). The results of this study have been published as an abstract only. A total of 75 patients were randomized and there was no difference in clinical outcome between the groups at 90 days. Details of diagnostic confirmation, the randomization procedure, allocation concealment, and outcome measures are not yet available. In a personal communication, one of the principal investigators has indicated that the complete results will be submitted to a peer-reviewed journal.

Risk of bias in included studies
CVT Group 1999 recruited patients from 15 hospitals in the Netherlands and the UK. Treatment allocation was concealed by using numbered packages containing prefilled syringes with nadroparin or identically appearing placebo. A computer program randomly allocated one of the numbered packages to each patient, according to a stratified block randomization schedule, with strata for ICH on the pretreatment CT scan, and for chronic intracranial hypertension. A minimization procedure was applied to allocate approximately equal amounts of control and placebo patients to the strata. An error in the randomization program caused temporary imbalance, which was corrected during the second half of the trial. Patients and doctors were blinded during the first three weeks of placebo-controlled treatment and at the first assessment at three weeks. The success of blinding was not examined. Follow-up treatment and assessment at 12 weeks were non-blinded. One patient (on placebo) with a wrong diagnosis was withdrawn after randomization. No patients were lost to follow-up. Baseline data were balanced (age, sex, treatment delay, number with Glasgow Coma...
Score < 8, seizures, focal deficits, number with ICH), except isolated intracranial hypertension (more in the placebo group) and infarcts on CT/MRI (more in the nadroparin group). Both factors were not significantly associated with outcome in univariate and multiple logistic regression analysis (de Bruijn 2001).

Einhaupl 1991 was a single centre study, performed in a large teaching hospital in Munich, Germany. Treatment allocation was concealed by using numbered sealed envelopes. Random assignment was done by a computer random number generator. The patients and the assessing physician were blinded. The treating physician who adjusted the heparin dosage was non-blinded. Placebo consisted of continuous saline infusion. The success of blinding was not examined. There were no withdrawals after randomization and no patients lost to follow-up. All patients were included in the analysis. Baseline data were balanced (age, sex, Glasgow Coma Score, CVT severity scale, number with ICH), except for treatment delay.

Effects of interventions
We presented results as relative risks with 95% CI and as absolute risk differences or absolute risk reductions (ARR). Odds ratios are also provided.

Primary outcome measures
Death from any cause at the end of the scheduled trial follow-up

Anticoagulant treatment was associated with a relative risk of death of 0.33 (95% CI 0.08 to 1.21, Figure 1). The absolute reduction in the risk of death was -13% (95% CI -27% to 1%)

Figure 1: Overall benefit or harm of (LMWH) heparin, outcome 1 death.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events Total</th>
<th>Control Events Total</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Einhaupl 1991</td>
<td>0 10 3 10 46.2%</td>
<td>0.14 [0.01, 2.45]</td>
<td></td>
</tr>
<tr>
<td>CVST Group 1999</td>
<td>2 30 4 29 53.8%</td>
<td>0.48 [0.10, 2.44]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>40 39 100.0%</td>
<td>0.33 [0.08, 1.28]</td>
<td></td>
</tr>
</tbody>
</table>

Total events 2 7
Heterogeneity: Chisq = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.60 (P = 0.11)
Death or dependency at the end of the scheduled trial follow-up period

In both trials, anticoagulant treatment was associated with a non-significantly reduced number of patients who were dead or dependent three months after the diagnosis of CVT. *Einhaupl 1991* did not formally assess dependency. Three (out of 10) patients died in the control group, and none died in the heparin group. All patients treated with heparin recovered fully, one with mild residual symptoms. One of the seven surviving patients in the control group had a CVT severity score of 3, indicating severe headache or mild paresis. The others had better outcomes. We classified all surviving patients in the control group as independent. In *CVT Group 1999* four of the 30 patients treated with nadroparin were dead (two patients) or dependent (two patients) after three months. In the control group there were four deaths and two patients were dependent. Meta-analysis showed a non-significant relative risk of 0.46 (95% CI 0.16 to 1.31) in death or dependency associated with anticoagulant therapy (Figure 2). The absolute reduction in the risk of death or dependency at follow-up was -13% (95% CI -30% to 3%).

Intention-to-treat analysis

One patient in the placebo group of *CVT Group 1999* had an incorrect diagnosis (arterial ischemic stroke). When the data from this patient were included in a full intention-to-treat analysis, the effect estimates for both primary outcomes did not materially change, nor did the overall conclusions.

Secondary outcome measures

Confirmed pulmonary embolism

There were no cases of confirmed pulmonary embolism. However, both trials each reported one patient in the placebo group with unconfirmed but probable pulmonary embolism. In *Einhaupl 1991* one patient had severe pulmonary
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infarction, but details of diagnostic confirmation were not available. In CVT Group 1999 one patient suddenly died after initial recovery, presumably due to massive pulmonary embolism. Autopsy was not performed.

Symptomatic intracranial hemorrhage (ICH)

In both trials, no new symptomatic ICHs were diagnosed after initiation of anticoagulant therapy, despite the fact that many patients who received heparin had some degree of ICH on their pre-treatment CT scans (three of 10 patients in Einhaupl 1991; 15 of 30 patients in CVT Group 1999). Einhaupl 1991 reported two patients in the control group with new ICHs but without clinical details. Since this study performed at least two routine CT scans in each patient, we classified these hemorrhages as asymptomatic.

Major extracranial hemorrhage

One patient on nadroparin treatment in CVT Group 1999 suffered a major non-fatal gastrointestinal hemorrhage. This amounts to a pooled relative risk of 2.9 (CI 0.12 to 68.5) and an absolute risk difference of 2% (95% CI -6 to 11, figure 3).

Figure 3: Severe haemorrhagic complications

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Treatment Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Weight</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Einhaupl 1991</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td>10</td>
<td>Not estimable</td>
</tr>
<tr>
<td>CVST Group 1999</td>
<td>1</td>
<td>30</td>
<td>0</td>
<td>29</td>
<td>2.90 [0.12, 68.50]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>40</td>
<td>39</td>
<td>100%</td>
<td>29</td>
<td>2.90 [0.12, 68.50]</td>
</tr>
<tr>
<td>Total events</td>
<td>1</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 0.66 (P = 0.51)</td>
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</tbody>
</table>

Sensitivity analysis

Since the data from the included studies were so sparse we performed a post-hoc sensitivity analysis including the data from the excluded trials (Maiti 1997; Nagaraja 1995). If we included these data, then the pooled relative risk for death would be 0.33 (95% CI 0.14 to 0.78). There were insufficient data to allow sensitivity analysis for death or dependency.
Discussion

Efficacy of anticoagulant treatment
The two small trials which met our predefined inclusion criteria showed a non-significant trend towards fewer deaths or dependency in patients treated with anticoagulants. However, the confidence intervals included no effect and the combined evidence failed to reach conventional statistical significance.

We excluded two other studies from the analysis (Maiti 1997; Nagaraja 1995). Maiti 1997 has only been published as an abstract and important details about the study design were not available. Nagaraja 1995 did not meet our predefined criterion: CVT was not diagnosed by angiography, MRI/MRA, or CT-venography. Nevertheless, it seems likely that most of these women had (puerperal) CVT. Interestingly, the small beneficial effect of heparin seen in the included trials was also observed in this study: two of the 28 controls died and no deaths occurred in the 29 patients treated with heparin. Therefore, these results provide some support to the efficacy of heparin in CVT.

The validity of meta-analysis of the two included studies might be questioned because different kinds of heparin were used (Benamer 2000). Einhaupl 1991 used unfractionated, intravenous, dose-adjusted heparin; CVT Group 1999 used subcutaneous, fixed dose, low-molecular-weight heparin (nadroparin). A Cochrane Review of 22 randomized trials among patients with leg-vein thrombosis showed a better efficacy and fewer hemorrhages of low-molecular-weight heparin compared with unfractionated heparin (van Dongen 2004). A recent post-hoc analysis of a large prospective cohort study of CVT suggested that low-molecular-weight heparin also leads to better outcomes and fewer hemorrhagic complications than unfractionated heparin in these patients (Coutinho 2010). In addition, results of a small randomized study which directly compared low-molecular-weight heparin with unfractionated heparin for CVT have been published as an abstract (Modi 2006). This study of 75 patients did not show any major differences in efficacy but final results have not yet been published. In summary, the differences in efficacy between low-molecular-weight heparin and unfractionated heparin, although significant in leg-vein thrombosis, are probably not very large, and combining both CVT trials seems justified as far as treatment is concerned. A second problem is the difference in
the timing of treatment. The average time from initial symptoms to treatment was about four weeks in *Einhaupl 1991*: 32 days in the heparin group, 25 days in the controls. In *CVT Group 1999* treatment started after an average of 10 days in the nadroparin group and 11 days in the control group. Some diagnostic delay in CVT is usual. In two non-randomized cohort studies, average delays of four and seven days were reported (*Ferro 2001; Ferro 2004*). The diagnosis can be difficult due to the variable and often non-specific symptoms. In addition, the diagnosis was more difficult before the advent of MRI. The long therapeutic delay in *Einhaupl 1991* may be caused by a diagnostic delay, although even with intra-arterial angiography a delay of four weeks from onset of symptoms to the start of treatment seems exceptionally long. This delay could also indicate that a subgroup of patients with more prolonged course was recruited, for instance patients who deteriorated after an initial favorable course without anticoagulant treatment.

**Pulmonary embolism**

One of our predefined outcomes was pulmonary embolism (PE). Two cases of clinically diagnosed PE occurred in the placebo groups, but data on diagnostic confirmation were not available. These cases point to a potential benefit of anticoagulants in CVT. Pulmonary embolism is not rare in CVT and might be caused by embolism from a thrombosed sinus or from simultaneous leg-vein thrombosis (*Diaz 1992*). The latter is not unlikely: many patients with CVT are in a prothrombotic state and often immobilized. As in leg-vein thrombosis an important benefit of anticoagulant treatment in CVT might be the prevention of pulmonary embolism.

**Intracerebral hemorrhage**

The main reason for many clinicians avoiding anticoagulants in CVT was the fear of hemorrhagic complications, notably intracerebral bleeding. Many patients with CVT have cerebral hemorrhages or hemorrhagic infarcts at the time of the diagnosis, before treatment (25% in *Einhaupl 1991*; 49% in *CVT Group 1999*). Yet, few cases of CVT with hemorrhagic deterioration after heparin have been published. In one study of seven patients two new intracerebral hemorrhages developed after anticoagulant treatment (*Gettelfinger 1977*). One patient received urokinase in addition to heparin and the other developed CVT while on prophylactic subcutaneous heparin (*Bousser 1997*). In two published case series
treated with heparin no new intracerebral hemorrhages occurred \cite{Ameri92; Bruckner98}, but in two other uncontrolled series intracerebral hemorrhage did occur in 3.6\% \cite{Ferro01} and 5.4\% \cite{Einhaupl91} of the anticoagulated patients. In the International Study on Cerebral Vein and dural sinus Thrombosis (ISCVT), the largest prospective cohort study on CVT, new intracerebral hemorrhages occurred in 33 of 520 patients (6\%) who were treated with heparin in therapeutic dose \cite{Ferro04; Girot07}. However, this study was not designed to assess new intracerebral hemorrhages after heparin therapy, and follow-up brain imaging was not performed in all patients. In the two trials included in this review no symptomatic intracerebral hemorrhages occurred after anticoagulant therapy in 40 patients. This suggests that the risk of intracerebral hemorrhage in patients with sinus thrombosis who are treated with anticoagulants is low. However, 0\% symptomatic intracerebral hemorrhages in 40 patients treated with (low-molecular-weight) heparin is associated with a 95\% confidence interval of 0\% to 9\%, thus an incidence of up to 9\% new intracerebral hemorrhages cannot be excluded.

Extracerebral hemorrhage
One major extracerebral hemorrhage occurred in a patient treated with low-molecular-weight heparin in CVT Group 1999. This rate (3.3\%) is within the range to be expected in any group of patients treated with heparin. In a Cochrane Review of 22 trials assessing heparin for leg-vein thrombosis, unfractionated heparin was associated with 2.1\% major hemorrhages and low-molecular-weight heparin with 1.0\% \cite{vanDongen04}.

Sensitivity analysis
Our post-hoc sensitivity analysis, including the data from the two trials which did not meet our eligibility criteria \cite{Maiti97; Nagaraja95}, were of interest but must be interpreted with great caution since they are potentially subject to bias. However, the effects observed were consistent with those from the included studies and provide limited additional support for our carefully worded conclusions.

Anticoagulation in pediatric patients
We did not identify any randomized trial that included pediatric patients and data on the safety of heparin in children from other studies are limited
As a result, it was not possible to provide an evidence-based recommendation from randomized trials on the use of anticoagulation in these patients. International guidelines tentatively recommend the use of anticoagulation in older children and in selected neonates (Monagle 2008; Roach 2008; Saposnik 2011) and heparin is being increasingly used in pediatric patients (deVeber 2001; Vieira 2010). A recent post-hoc analysis of a prospective cohort study of 162 pediatric cases of CVT showed that protocol-based anticoagulant treatment (heparin, enoxaparin and warfarin) was associated with a significant reduction in thrombus propagation (Moharir 2010) and was associated with new or increased bleeding in 6%, all non-fatal bleeds. Propagation was significant in that it was associated with new venous infarcts in 10% of neonates and 40% of children and with worse clinical outcome in children (P = 0.053). While these data provide some support for the use of anticoagulation in children, a randomized trial seems warranted, especially in neonates.

Authors’ conclusion

Implications for practice
Anticoagulant treatment in patients with cerebral venous sinus thrombosis appears to be safe and is associated with an apparent reduction in the risk of death or dependency which did not reach statistical significance. In the absence of more information from randomized trials clinicians will need to base their treatment decisions on the limited information available.

Implications for research
Although the estimated pooled risk reductions did not reach statistical significance, patients and doctors may be reluctant to embark upon a new trial in adult patients that includes a placebo group. International guidelines recommend the use of heparin as the primary treatment of patients with CVT, regardless of the presence of baseline intracerebral hemorrhagic lesions (Einhaupl 2010; Saposnik 2011), and most physicians follow this recommendation (Ferro 2004). In pediatric patients, especially neonates, a randomized trial seems warranted.
Large consecutive cohort studies have helped to identify subgroups of patients with a poor prognosis (Ferro 2004). In such patients randomized trials testing more aggressive, and probably more hazardous, therapies such as local (direct) thrombolysis or thrombosuction, are justified and needed.

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References

References to studies included in this review

CVT Group 1999

Einhaupl 1991

References to studies excluded from this review

Maiti 1997

Nagaraja 1995

References to studies awaiting assessment

Modi 2006

Additional references

Ameri 1992

Benamer 2000

Bousser 1985

Bousser 1997

Bousser 2007

Bruckner 1998

Coutinho 2010

de Bruijn 2001
Anticoagulation for CVT: Cochrane review

deVeber 2001

Diaz 1992

Einhaupl 2010

Ferro 2001

Ferro 2004

Gettelfinger 1977

Girot 2007

Moharir 2010

Monagle 2008

RevMan 2008

Roach 2008

Saposnik 2011

Stam 2005

van Dongen 2004

Vieira 2010

Villringer 1994