Letter by Cundiff Regarding Editorial, “Cerebral Venous Thrombosis: Another Heparin Controversy”

To the Editor:

My opinion piece in Stroke challenged the evidence basis for anticoagulant drug treatment for cerebral venous thrombosis (CVT).1 Thanks to Dr Selim2 for his rebuttal.

Based on my systematic review of the limited available evidence divulged by CVT study authors in published articles and personal e-mails, my article detailed the case against anticoagulants:

- Anticoagulants for CVT are not evidence based to be effective or safe.
- Anticoagulants increase risk of major extracranial and intracerebral hemorrhage (ICH).
- The risk of venous thrombosis recurrence was significantly higher while CVT patients were taking warfarin compared with while they were not taking warfarin.

Dr Selim2 concedes that “the efficacy of anticoagulation in CVT has not been unequivocally proven.” However, he provides justification for anticoagulants based on the theory that they can prevent CVT propagation and thereby prevent ICHs. Although full-dose heparin has not been shown to prevent ICH, it is clear from published data that 2.6% of patients with CVT receiving full-dose heparin had new ICHs or increased volume of ICHs (17/643) and 2.3% of patients with CVT had major extracranial bleeding (14/598). As Dr Selim’s2 only rebuttal to these specific data regarding anticoagulation status and clinical outcomes, he cited the CVT meta-analysis, which included 2 small randomized controlled trials (RCTs; 40 patients anticoagulated—4 (10%) had major bleeding): “The Cochrane investigators concluded that anticoagulant treatment for CVT seems to be safe even in patients with ICH.”

Dr Selim2 gives a favorable analysis of the RCT of Einhaupl et al3 without rebutting any of my criticisms:

- The long delay after CVT diagnosis and before the treatment was started (mean delays: 33 and 25 days for the heparin and placebo groups, respectively) makes it highly dubious that anticoagulation accounted for the difference in mortality.
- In a heparinized pregnant woman, the stillbirth of a 38-week-old fetus, attributed to the anticoagulant, should have been counted as a death in the treatment arm of the trial.
- One patient in the placebo arm of the trial was treated with heparin based on a clinical diagnosis of pulmonary infarction and subsequently died. With no premorbid definitive diagnosis of pulmonary infarction and no autopsy reported, this case should not have been counted as a death in the placebo arm of the study.

Dr Selim2 wrote, “A retrospective review by the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT) also showed a nonsignificant but definite trend toward improvement with anticoagulation.” He cited a trend favoring acutely heparinized patients. However, the outcomes (survival, dependence) were 18 months after hospitalization—highly invalid.3 Dr Selim2 did not address my finding, not published in an ISCVT article but conceded to be correct by the ISCVT authors, that full-dose heparin was associated with increased risk of hospital mortality relative to no full-dose heparin (deaths: full-dose heparin, 25/520 [4.8%] versus no full-dose heparin, 2/104 [1.92%]; odds ratio, 2.5; 95% confidence interval, 0.58–10.7; P=0.20).4

Among the limitations of my opinion piece, Dr Selim2 cited the lack of data that I could obtain. However, the fact that almost all anticoagulation for CVT studies in the literature had major gaps in reporting of important data and most authors were not forthcoming with missing data when it was requested should cast doubt on the case for anticoagulating patients with CVT.

Dr Selim2 concludes, “…the existing evidence-based guidelines for management of CVT would benefit from more evidence.” I agree. First, thought leaders in neurology should demand that the authors of CVT RCTs and observational studies included in this review (especially those published after 2000) disclose any missing data regarding anticoagulation status and clinical outcomes. Then, to replace my anticoagulants for CVT opinion piece,1 an official systematic review of the RCT and observational study evidence could be published. At that point, medical scientists could openly discuss whether there is an evidence basis for anticoagulation treatment for CVT. If anticoagulants are ineffective and dangerous for CVT as the limited evidence suggests, the standard of care should change. If the benefit to harm ratio remains in doubt, an appropriately powered placebo controlled RCT should be implemented.

Disclosures

None.

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