Evidence-Basis for Anticoagulants for Cerebral Sinus Venous Thrombosis?

To the Editor:

The recent case of cerebral sinus venous thrombosis (CSVT) in the US Secretary of State Hillary Clinton brought my attention to articles that lay out the evidence-basis for the use of full dose heparin and oral anticoagulant drugs for CSVT. Unfortunately, articles published in Stroke by investigators from the International Study on Cerebral Vein and Dural Sinus Thrombosis (ISCVT), a large prospective observational study, have failed to report important evidence against the hypothesis that anticoagulants reduce morbidity and mortality of patients with CSVT. The following points have been missed specifically:

1. Canhão et al. did not report the odds ratios of heparinized versus nonanticoagulated patients regarding survival at discharge and at last follow-up, new central nervous system bleeding during hospitalization, and other clinical outcomes.

2. Although Canhão and other ISCVT investigators reported the heparinization status of 27 out of 624 patients who died in the study (25 out of 27 deaths were in heparinized patients), they did not report the number of patients given and not given full dose heparin or if any nonheparinized patients were diagnosed at autopsy. Apparently, 1 of 2 nonheparinized patients that died was diagnosed at autopsy, so no clinical decision was made not to anticoagulate. Consequently, readers could not know whether heparin was associated with good or bad outcomes.

3. Coutinho et al. used the same ISCVT database to make the case for recommending low molecular weight heparin instead of unfractionated heparin in CSVT patients. Fortunately, given the nature of the low molecular weight heparin versus unfractionated heparin comparison, this article had to reveal the number of nonanticoagulated and heparinized patients (104 versus 520).

4. I calculated the odds ratio for mortality in heparinized versus nonanticoagulated full dose patients (excluding the patient diagnosed at autopsy) using data from the above 2 ISCVT articles (odds ratio, 5.15; 95% confidence interval, 0.69–38.5; P=0.08). This indicates a strong trend toward heparin increasing mortality. I could not calculate the odds ratios regarding anticoagulation for the other clinical outcomes because data were not available.

5. Of interest regarding the Hillary Clinton case was that, for ISCVT patients ≥65 years old, 49% died or became dependent by 6 months versus 9% for patients <65 years old. Hillary Clinton is 65 years old. Of 46 patients ≥65 years old alive at discharge from the hospital, 2 (4.3%) patients later died of hemorrhage (1 hemorrhagic stroke and 1 systemic hemorrhage), while still taking oral anticoagulants.

Coutinho et al. presented the evidence-basis for heparin and oral anticoagulants for CSVT in a Cochrane Review and in Stroke. This meta-analysis of 2 small randomized controlled trials reported a non-significant risk ratio (RR) for death (risk ratio, 0.33; 95% confidence interval, 0.08–1.28). However, the death rate in the placebo group of these small trials conducted in the 1980s and 1990s was almost 18x higher than in nonanticoagulated patients from the larger and more recent ISCVT (17.9% [7 out of 39 patients] versus 0.96% [1 (excluding the autopsy diagnosed patient) out of 104 patients]). More frequent and better diagnostic imaging has increased the incidence of CSVT, including much milder cases. Better supportive care may have also improved outcomes.

The ISCVT authors should present all of the clinical outcome comparisons in anticoagulated versus nonanticoagulated patients and explain why they should or should not withdraw their case for anticoagulant treatment for patients with CSVT.

Disclosures
None.

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