Evidence Basis for Anticoagulants for Cerebral Sinus Venous Thrombosis? Reply to David K. Cundiff

To the Editor:

Dr David K. Cundiff states that the several publications of the International Study of Cerebral Vein and Dural Sinus Thrombosis (ISCVT) in the Stroke journal failed to provide evidence against the hypothesis that anticoagulants reduce morbidity and mortality in patients with cerebral vein and dural sinus thrombosis (CVT). He goes on by listing 5 points that have been specifically missed.

ISCVT was a cohort observational study, the primary objective of which was to describe the prognosis of CVT and its risk factors. It was not primarily designed to evaluate therapeutic interventions. Treatments were left to the choice of the local investigations without any interference from the Steering Committee of ISCVT. For certain interventions, there was enough variation to allow a naturalistic case–control evaluation of treatments. These secondary analyses of the ISCVT data must be regarded with caution because of the risk of bias and overestimation of risk and benefits common in secondary analysis and case–control studies.

ISCVT investigators are completely aware of the limitations of their results on treatment analyses. As every clinical researcher knows, in prospective and observational studies, treatment is a variable that often may be confounded by indication. A large body of evidence has also shown that in prospective studies, even multivariate analysis rarely shows significant effect of treatment in the outcome. In ISCVT, the majority of patients were anticoagulated, and therefore, there is no variation to allow case–control comparisons for this intervention because of the lack of statistical power. Accordingly, it is absolutely inappropriate to draw any therapeutic inferences on anticoagulation versus nonanticoagulation based on ISCVT. That is why we consider that the 5 points raised by Dr Cundiff are based on superficial and scientifically unsound analysis of ISCVT published data.

Concerning his comments on the article of Canhão et al addressing the frequency of acute death and its causes, we do not know the sources of information used by Dr David Cundiff. Indeed, 25 of 27 dead patients were treated with heparin. Even the patient with CVT diagnosis confirmed by autopsy was treated with heparin. The odds ratio for acute death in patients treated with heparin was 2.6 (with 95% confidence intervals of 0.6 to 11.1; \( p=0.29 \)), different from those calculated by Dr David Cundiff. He further stated that “readers could not know whether heparin was associated with good or bad outcomes.” No thoughtful reader could expect to have this type of information with the ISCVT study.

Finally, Dr Cundiff made some considerations about the predictive effect of age on the prognosis of CVT, illustrating the case of Hillary Clinton, misusing the information given in the ISCVT article addressing the effect of age on the prognosis of CVT. As it was clearly exemplified by the ISCVT, there are multiple factors determining the prognosis of CVT. The prediction of CVT can be individualized. Indeed, ISCVT investigators developed and validated a model and score to provide individual predictions. A wise physician will certainly use all the information provided by the ISCVT to tell a woman, experiencing an acute CVT, with headache as clinical presentation, not being in coma or having mental disturbances, nor having hemorrhagic lesions or cerebral deep venous thrombosis, that she will most likely have a good prognosis, despite her age.

Dr Cundiff has already been notified via E-mail by the principal investigator of ISCVT that we are currently analyzing the risk of intracerebral bleeding in patients who had a repeated brain scan. In this publication, we will also report the clinical outcomes of anticoagulated and nonanticoagulated patients. Unfortunately, we cannot report on systemic bleedings because these were not collected, except fatal ones. We hope to have the analysis finished and the publication drafted for circulation among ISCVT investigators by the end of next September.

Disclosures

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