Letter to the Editor

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Letter by Stam Regarding Article, “Anticoagulants for Cerebral Venous Thrombosis: Harmful to Patients?”

To the Editor:

In an opinion piece published recently in this journal, Dr Cundiff tries to convince the readers that anticoagulants may be not effective and even harmful to patients with cerebral venous thrombosis (CVT). By doing so, he holds a minority opinion against current practice and published guidelines. Therefore, his methods and arguments deserve close scrutiny. Although presented as an opinion statement, the article has all characteristics of a systematic review: the author went at great lengths to identify all studies of CVT, published from 1991 to 2013, which reported anticoagulants treatment and clinical outcomes. Not surprisingly in a rare disease like CVT, most of these studies are case series. From the 39 studies identified, only 6 are randomized trials. In these 39 studies, 2211 patients were treated with full-dose heparin, of whom 202 (9.1%) died. Among the patients not treated with heparin, the death rate was 14.0% (78 of 557). It can be questioned if statistical analysis of this material makes sense at all, but Dr Cundiff applied a χ² test, which yielded an impressive P value of 0.0007. Most scientists would stop here and admit defeat—heparin is clearly superior—but not Dr Cundiff, who embarks on a long exercise in creative data analysis to show that heparin may be harmful after all. To achieve this, he divided the 39 studies in 2 subgroups, across an arbitrary point in time: the year 2000. Only the studies published after 2000, he analyzed again: now the mortality is nonsignificantly greater after heparin treatment (9.7% versus 8.8%; P=0.77). Of course, this subgroup analysis backfires: in the studies published before 2000, the difference in mortality is now even greater: 4.3% after heparin and 15.2% without heparin. This result is not analyzed by Dr Cundiff, but by applying his method it gives a P value of 0.00003. The paradoxical outcome of the arbitrary dichotomy of Dr Cundiff is that heparin worked well before 2000, and thereafter it miraculously lost its effectiveness. The latter is easily explained by the fact that after 2000 nearly all patients (95.1%) received full dose heparin, as opposed to only 33.7% before 2000. It is likely that the small minority of cases (4.9%) not treated with heparin after 2000 constitute a highly selected group, which makes any comparison with the heparin-treated patients meaningless.

There are 2 major objections to the approach by Dr Cundiff: first, it is impossible to draw reliable conclusions about treatment efficacy from case series. Second, by constructing subgroups, one can demonstrate about anything.

The only way to obtain an unbiased estimate of a treatment effect is to analyze the data from randomized trials. Dr Cundiff omitted such an analysis, although the data are all present in his article. Of the 6 trials identified, 4 compared patients treated with heparin to controls treated without anticoagulants. If we analyze these trials with Cundiff’s approach (incorrectly, but for the sake of the argument), the mortality is 5.6% (5 of 89) among the patients treated with heparin, versus 19.5% (17 of 87) among controls, again a significant result in favor of heparin (χ²; P=0.005). Actually, in our Cochrane meta-analysis, we excluded 2 of these trials because of poor methodology. The 2 remaining trials give the best estimate of the effect of heparin in CVT: a nonsignificant reduction of poor outcomes (death or dependency) of 13% (95% confidence interval, 30 to −3). This result was already known in 2002.

In conclusion, the opinion of Dr Cundiff that heparin may be harmful for patients with CVT is not supported by the data he presents. Analysis of the available evidence supports the common practice and the guidelines: patients with CVT, even in the presence of hemorrhagic infaracts, have a better chance of a good outcome when initially treated with full-dose (unfractionated or low-molecular weight) heparin, unless there is a clear contraindication.

Disclosures

None.

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Letter by Stam Regarding Article, "Anticoagulants for Cerebral Venous Thrombosis: Harmful to Patients?"
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