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Antifibrinolytic treatment in subarachnoid hemorrhage: Harmful or beneficial?

We read with interest the article "Antifibrinolytic therapy in aneurysmal subarachnoid hemorrhage increases the risk for deep venous thrombosis: a case-control study" by Foreman et al., describing the secondary outcome analysis of a case-control study, which had looked at genetic polymorphisms in the renin angiotensin system in relation to different outcome measurements [1]. Their results showed that the risk of deep venous thrombosis (DVT) was increased when ε-aminocaproic acid (EACA) was given early after aneurysmal subarachnoid hemorrhage (SAH). In 2008, Starke et al. reached the same conclusion, showing an 8-fold increased risk of (symptomatic) DVT with the use of short-term EACA [2].

This article is an important contribution. Matching on a history of DVT or thromboembolic problems and information with respect to history of DVT however, might have given more insight into the relation between EACA, medical history and DVT. Moreover, rigorous reporting of the indications of EACA, such as age, severity of SAH and time interval since admission, along with the physicians discretion, could have strengthened the study. Interestingly, no statistical analysis was done to compare the screened patients with EACA who developed DVT (35%; 7/20), with the rate of DVT in screened patients without EACA (11%; 3/28). In addition, in the control group only four patients used EACA (20%), whereas in the total group of eligible controls ($n = 118$), 50 patients used EACA (42%). Apparently, a large number of patients who were potential candidates for the control group were not included for analysis, and it is unclear why these were not selected. The matching between groups could have caused this effect. Lastly, we are missing the information whether there was any difference in the dosage of EACA in those with and without DVT.

The use of antifibrinolytics, like EACA, is justified because they significantly reduce the number of recurrent bleedings [3,4]. However, antifibrinolytics may also induce DVT formation and, when given for several days, increase the risk for delayed cerebral ischemia (DCI) [3]. The randomized controlled trial by Hillman et al. showed that early and short-term treatment appears not to increase the risk of DCI, but unfortunately it was underpowered to show an improvement of functional outcome [5]. So, despite all the current knowledge, it is still not proven whether antifibrinolytic therapy is harmful or beneficial for patients. The reason why antifibrinolytic treatment is gaining more popularity is based on the knowledge that the risk for recurrent bleeding is the highest in the first few hours after the initial hemorrhage [6]. As a consequence, an ultra-early and short-term administration of antifibrinolytics might be maximally beneficial in reducing recurrent bleeding with the least risk for drug-related complications. Currently, a randomized controlled trial is enrolling patients in the Netherlands, examining whether tranexamic acid, given directly after the diagnosis of SAH and continued until aneurysm treatment, with a maximal time interval of 24 h, leads to a better functional outcome (ULTRA trial, which stands for ultra-early tranexamic acid after subarachnoid hemorrhage) [7]. The first results are expected in 2019.

In conclusion, it is certainly prudent to take care when administering antifibrinolytic agents to aneurysmal SAH patients, especially because of the increased risk for DVT and DCI, and not yet proven better functional outcome. But the results of the ULTRA-trial must be awaited until we can tell whether ultra-early and short-term antifibrinolytic treatment leads to a better functional outcome.

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