



Neurosurgical Forum
LETTERS TO THE EDITOR

Short-term ϵ -aminocaproic acid treatment and endovascular coil embolization

TO THE EDITOR: We read with interest the article by Malekpour and colleagues⁶ (Malekpour M, Kulwin C, Bohnstedt BN, et al: Effect of short-term ϵ -aminocaproic acid treatment on patients undergoing endovascular coil embolization following aneurysmal subarachnoid hemorrhage. *J Neurosurg* [epub ahead of print June 17, 2016; DOI: 10.3171/2016.4.JNS152951]), describing short-term treatment with ϵ -aminocaproic acid (EACA) in a consecutive case-control cohort undergoing endovascular treatment. The authors found no reduction in the risk of pretreatment recurrent bleeding in the EACA treatment group. Furthermore, short-term treatment showed no increase in pulmonary embolism and deep venous thrombosis (DVT), either in the risk of vasospasm, clinical stroke, or radiological infarction.

This article is important: it is one of the few reports describing short-term EACA treatment before endovascular aneurysm occlusion. Interestingly, the authors found no increase in the risk of DVT, which is in contrast to the findings of Foreman et al.² and Starke et al.⁷ This is especially remarkable because the authors continued EACA treatment until the start of the endovascular procedure, which is in contrast with previous reports in which EACA treatment was discontinued several hours before endovascular aneurysm treatment^{5,7} because of the potential risk of more thromboembolic complications during aneurysm treatment. Some points that might have strengthened the study are data on the total average dose of administered EACA, the mean duration of administration of EACA, and whether EACA treatment led to more risk of thromboembolic complications during aneurysm treatment.

Furthermore, the authors report that short-term treatment resulted in no increase in the risk of vasospasm, clinical stroke, or radiological infarction. However, a clear definition of vasospasm and clinical stroke was not provided, nor were how and when radiological infarction was defined and which modality was used. Hence, interpretation of these results remains difficult.

It is remarkable that the recurrent bleeding percentage was low when compared to findings reported in the litera-

ture: 3.1% versus 4.1% in the no treatment versus EACA treatment group, respectively. The authors report some factors that might have led to these low percentages: first, a decrease in the time interval between aneurysm rupture and treatment over the years; and second, interhospital transfers of some patients. A recent study by Germans et al.³ did indeed show that early recurrent bleeding occurs in 12% of individuals, with an additional 4% of patients having possible recurrent bleeding. Also, Germans et al.³ found that up to 40% of patients had recurrent bleeding before reaching a treatment center. Therefore it might be possible that out-of-hospital recurrent bleeding and that occurring during interhospital transfer was underreported. Nevertheless, Germans et al.³ found that the median time from onset of hemorrhage to recurrent bleeding was only 3 hours, precluding a positive effect of even more expeditious treatment.

Therefore, it appears that the start of antifibrinolytic treatment as early as possible is warranted, preferably as soon as the diagnosis of subarachnoid hemorrhage (SAH) is made, and only for a very short period of time, up until the causative aneurysm is treated. In this way the beneficial effects on recurrent bleeding are maximized, and the side effects of long-term treatment are minimized, as proposed in the recent update on the use of tranexamic acid in patients with SAH.¹

An ongoing, randomized, controlled trial (the Ultra-Early Tranexamic Acid After Subarachnoid Hemorrhage [ULTRA] trial) is currently enrolling patients in the Netherlands,⁴ and is registered at the Dutch Trial Registry (NTR3272) and clinicaltrials.gov (NCT02684812). This study should provide an answer to the question of whether ultraearly (as soon as possible after diagnosis) and short-term (until aneurysm treatment—with a maximum of 24 hours) tranexamic acid treatment leads to a better functional outcome. The final results are expected in 2019.

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Disclosures

The authors report no conflict of interest.

Response

We sincerely appreciate the comments by Dr. Post and colleagues. The current lack of prospective, randomized data regarding short-term antifibrinolysis in the setting of aneurysmal SAH leaves important clinical questions unanswered; their upcoming randomized controlled trial (i.e., the ULTRA trial) should assist in answering these clinical questions.

In our study, the data points for the incidence of vasospasm, clinical stroke, and radiological infarction were collected from the medical records prospectively during the course of the patient's hospitalization, based on clinical documentation. Vasospasm and clinical stroke (the latter defined as transient vs permanent focal neurological findings that could not otherwise be attributed to another source) were determined based on the clinical judgment of the neurosurgical team.

We agree that our findings differ from those reported in other similar series regarding DVT rates. Both cited studies,^{3,4} however, included microsurgically and endovascularly treated patients, whereas our study included only endovascularly treated patients, thus representing different patient populations.

More aggressive DVT screening protocols would have found more thromboses that otherwise would have been clinically silent and never required treatment. The control versus study group in Foreman et al.'s study³ was screened at a similar rate (35.1% vs 39.4%, respectively), suggesting that some of the DVTs in the antifibrinolytic group potentially were clinically silent and that these were thus incidental findings. Finally, differences in DVT prophylaxis protocols between institutions may contribute to the different rates of DVT detection.

The rehemorrhage rate in our study may have been lower than expected. This finding is probably due to limitations of our study design. Rehemorrhages prior to admission or in transit were unlikely to be captured; our hospital is the primary aneurysm referral site for a large geographic area. We agree that the optimum strategy to maximize benefit from antifibrinolysis is to initiate it as early as possible and to combine its use with early aneurysm treatment to avoid the negative effects of long-term antifibrinolysis administration.

The antifibrinolytic agent of choice remains elusive, yet tranexamic acid may carry advantages over EACA because it is 10 times more potent, does not affect the blood coagulation parameters, and more readily crosses the blood-brain barrier.^{1,2} We appreciate the authors' insights, especially given their ongoing work in this area, and also eagerly await the results of the ULTRA trial to see if such an application of antifibrinolysis does indeed provide clinical benefit.

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