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Impact of a Protocol for Acute Antifibrinolytic Therapy on Aneurysm Rebleeding After Subarachnoid Hemorrhage

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Background and Purpose— ϵ -Aminocaproic acid (EACA) is an antifibrinolytic agent used to prevent rebleeding in aneurysmal subarachnoid hemorrhage. Although studies have found that a decrease in rebleeding with long-term antifibrinolytic therapy is offset by an increase in ischemic deficits, more recent studies have indicated that early, short-term therapy may be beneficial.

Methods—We instituted a protocol for acute EACA administration starting at diagnosis and continued for a maximum duration of 72 hours after subarachnoid hemorrhage onset. We compared 73 patients treated with EACA with 175 non-EACA-treated patients. We sought to identify differences in the occurrence of rebleeding, side effects, and outcome.

Results—Baseline characteristics were similar in the 2 groups. There was a significant decrease in rebleeding in EACA-treated patients (2.7%) versus non-EACA patients (11.4%). There was no difference in ischemic complications between cohorts. There was a significant 8-fold increase in deep venous thrombosis in the EACA group but no increase in pulmonary embolism. There was a nonsignificant 76% reduction in mortality attributable to rebleeding, a 13.3% increase in favorable outcome in good-grade EACA-treated patients, and a 6.8% increase in poor-grade patients.

Conclusions—When used acutely, short-term EACA treatment resulted in decreased rebleeding without an increase in serious side effects in our selected group of patients. Randomized placebo-controlled trials are needed to determine whether acute antifibrinolytic therapy should be accepted as the standard of care in all patients. (*Stroke*. 2008;39:2617-2621.)

Key Words: aminocaproic acid ■ antifibrinolytic therapy ■ rebleeding ■ aneurysm ■ subarachnoid hemorrhage

When untreated, the rate of rebleeding after aneurysmal subarachnoid hemorrhage (aSAH) is 4% to 20% within the first 24 hours, which results in serious morbidity and mortality.^{1,2} Antifibrinolytic therapy before delayed surgical aneurysm repair was used in many centers but was largely abandoned when trials demonstrated that the reduction in rebleeding with prolonged antifibrinolytic treatment was offset by an increase in ischemic deficits.³

If antifibrinolytic agents are used acutely, when patients are at the greatest risk of rebleeding, but are stopped before the window of vasospastic injury (days 3 to 14),⁴ such treatment may improve outcome without increasing ischemic deficits. Studies have indicated that acute antifibrinolytic therapy may reduce rebleeding, but no studies have performed an in-depth analysis of side effects.^{2,5} We hypothesized that a protocol of acute antifibrinolytic therapy with ϵ -aminocaproic acid (EACA) would result in decreased rebleeding without an increase in serious side effects.

Methods

Patients

Prospectively obtained outcomes in 248 aSAH patients enrolled in the Institutional Review Board–approved SAH Outcomes Project between May 2003 and October 2004 were reviewed.^{6,7} Starting in May 2003, patients with SAH received EACA at the time of diagnosis. EACA (4 g IV) was administered as a loading dose followed by 1 g/h, with cessation of infusion 4 hours before angiography for a maximum duration of 72 hours after SAH onset. Patients with ECG changes, cardiac troponin elevations, or symptoms of thromboembolic disease were excluded from the EACA protocol. The intention was to administer EACA to all patients unless their arrival time was near the window for angiography or they had acute thromboembolic symptoms as described. All patients were treated acutely (arrival <3 days after aSAH or treated with EACA for <3 days). Patients later found to have nonaneurysmal SAH on angiography were removed from the protocol. All patients received nimodipine, compression stockings, and enoxaparin or subcutaneous heparin. Lower-extremity Doppler ultrasound was performed at 7 to 10 days and on symptomatic patients.

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Table 1. Baseline Characteristics of EACA- and Non-EACA-Treated Patients

	Non-EACA	EACA	Significance (<i>P</i> Value)
	175	73	
Mean age, y	57±15	56±15	0.680
Female sex	124 (71%)	54 (74%)	0.619
Medical history			
Smokers	89 (51)	40 (55)	0.572
Hypertension	90 (51)	40 (55)	0.629
Cardiovascular disease	26 (15)	9 (12)	0.602
Diabetes mellitus	16 (9)	6 (8)	0.816
Kidney disease	4 (2)	3 (4)	0.429
DVT	4 (2)	3 (4)	0.429
Anticoagulation therapy	6 (3)	2 (3)	0.780
Antiplatelet therapy	20 (11)	12 (16)	0.283
Hunt-Hess grade			
I	31 (18)	10 (14)	0.707
II	43 (25)	15 (21)	
III	49 (28)	21 (29)	
IV	27 (15)	12 (16)	
V	25 (14)	15 (20)	
Modified Fisher Grade			
2	61 (35)	21 (29)	0.644
3	93 (53)	42 (57)	
4	21 (12)	10 (14)	
Aneurysm characteristics			
Admission angiography	164 (94)	67 (92)	0.583
Mean size, mm	7±4	7±4	0.345
Size >10 mm	37 (23)	12 (18)	0.384
Surgery			
Mean day of surgery	1.21±0.85	1.27±1.0	0.639
Clip	99 (58)	47 (64)	0.424
Coil	46 (27)	13 (18)	
Clip and coil	5 (2)	1 (1)	

Categorical variables are represented as No. (%). Continuous variables are presented as mean±SD.

Study Outcomes

We have previously defined rebleeding,⁸ symptomatic vasospasm,⁹ infarction due to vasospasm,⁶ and myocardial ischemia.⁷ Deep venous thrombosis (DVT) was determined by Doppler ultrasonography. Outcome was assessed with the Modified Rankin Scale score at discharge and at 3 months.¹⁰ Discharge and 3-month outcomes were obtained in 100% and 90.3% of patients, respectively.

Statistical Analysis

Analysis was performed with the unpaired *t*, χ^2 , and Fisher's exact tests, as appropriate. Kaplan-Meier cumulative survival curves for the primary end point of rebleeding were used to compare patient cohorts. The log-rank test was used to assess differences in survival curves, and Cox regression was used to assess hazard ratios. Multiple studies were compared with Mantel-Haenszel pooled χ^2 (Review

Table 2. Outcomes in EACA- and Non-EACA-Treated Patients

	Non-EACA Group n=175	EACA Group n=73	Significance (<i>P</i> Value)
Acute rebleeding*	17 (9.7)	2 (2.7)	0.045
Rebleeding in Hunt-Hess grade I–III patients†	8 (6.5)	0 (0)	0.074
Rebleeding in Hunt-Hess grade IV and V patients†	12 (23.1)	2 (7.4)	0.073
Overall rebleeding	20 (11.4)	2 (2.7)	0.019
Ischemic deficits			
Cerebral infarction	46 (26)	19 (26)	0.966
Infarct due to vasospasm	18 (10)	5 (7)	0.395
Infarct, other causes	30 (17)	16 (22)	0.378
Symptomatic vasospasm	42 (24)	18 (25)	0.912
Follow-up angiography	97 (55)	37 (50)	0.495
Angiographic spasm	56 (57)‡	23 (62)‡	0.641
Cerebrovascular occlusion	4 (1.5)§	0	0.371
Extracranial thrombosis			
Lower-extremity DVT	2 (1.1)	7 (9.6)	0.003
Pulmonary embolism	5 (2.9)	1 (1.4)	0.487
Upper-extremity/neck venous thrombosis	6 (3.4)	7 (9.6)	0.047
Upper-extremity/neck arterial thrombosis	3 (1.7)	0	0.35
Total thrombosis	16 (9.2)	15 (20.5)	0.015
Favorable 3-month Modified Rankin Scale score			
Hunt-Hess grades I–III	80 (65)	36 (78)	0.10
Hunt-Hess grades IV and V	8 (15)	6 (22)	0.45

Categorical variables are represented as No. (%).

*Rebleeding within 72 hours of admission.

†Hunt and Hess grade on admission.

‡Percentage of patients who had follow-up angiography who had angiographic spasm.

§Percentage of patients who had cerebrovascular occlusion on admission or follow-up angiography.

Manager 4.2, Copenhagen, The Cochrane Collaboration, 2003). Modified Rankin Scale scores were dichotomized, with 0 to 3 signifying a favorable outcome and 4 to 6 a poor outcome. The last known outcome was used for statistical purposes. Probability values ≤ 0.05 were considered statistically significant. Given our sample size and an $\alpha=0.05$, we estimated our power to detect a difference in rebleeding incidence of 10.5% in non-EACA-treated and of 3% in EACA-treated patients, 11.5% and 2.5%, 12.5% and 2%, or 13.5% and 1.5%, to be 45%, 66%, 80%, and 90%, respectively.

Results

Cohort Characteristics and Treatment

Seventy-three patients who were treated with EACA during this time period were compared with 175 non-EACA-treated patients. There was no significant difference in baseline characteristics between the groups (Table 1) and no difference in aneurysm location ($P=0.44$, data not shown).

The mean number of days between aSAH and treatment with EACA was 0.52 ± 2 , and mean treatment duration was

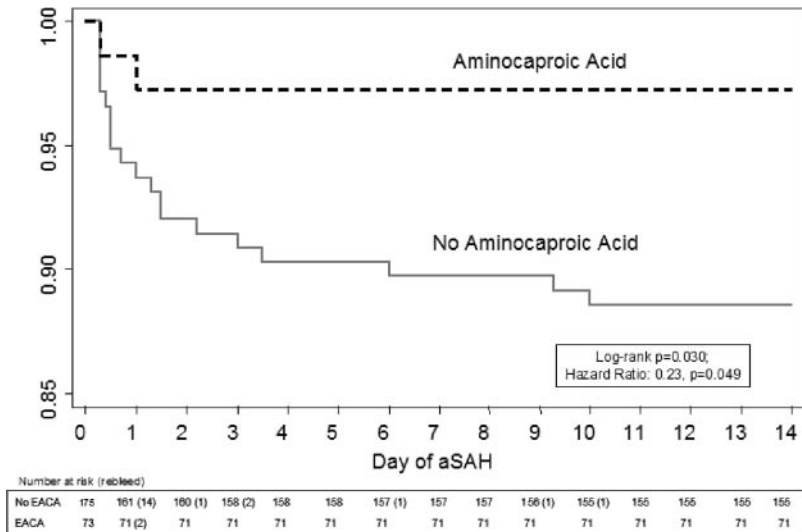


Figure 1. Cumulative rebleeding-free survival according to antifibrinolytic group.

15.3±16 hours. Twenty-nine patients received EACA before transfer, and 25 patients received 1 dose, 5 patients received 2 to 4 doses, and 43 patients received 5 or more doses. As the protocol was adopted, the proportion of patients treated with EACA increased over time: 32% of patients received EACA from October 2003 to April 2004, and 60% of patients received EACA from May to September 2006.

Overall Outcome

In total, 52% of patients had favorable 3-month outcomes. Four percent of patients died of rebleeding, and 50% of patients who had rebleeding died. There was a 13.3% increase in favorable outcome in EACA-treated patients of Hunt and Hess grades I through III (P=0.10) and a 6.8% increase in EACA-treated patients of Hunt and Hess grades IV and V (P=0.45).

Rebleeding

Nine percent of patients had rebleeding, and 86% of such episodes occurred within 72 hours of aSAH onset (mean day

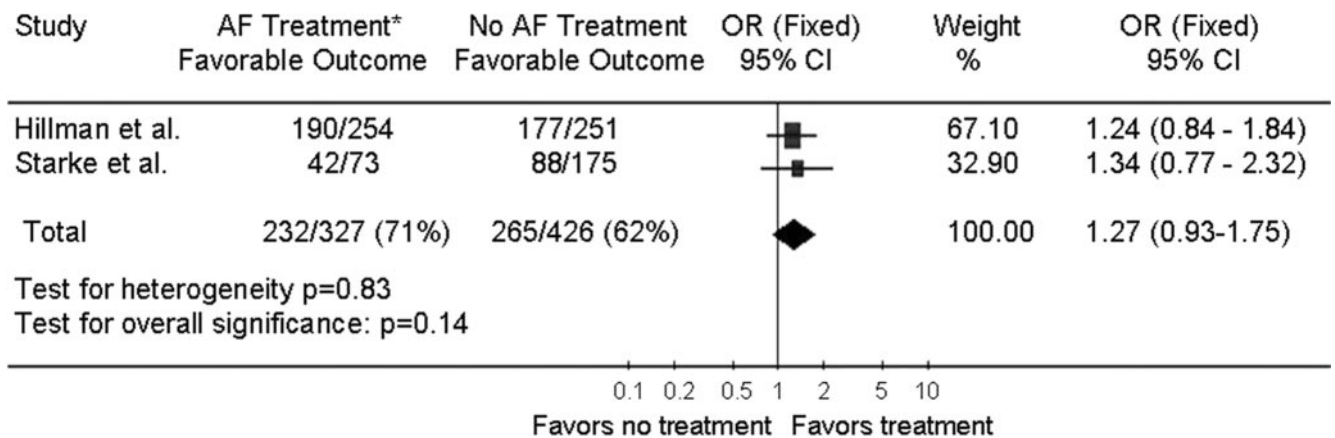
of rebleed, 1.7±2.9). In EACA-treated patients, 2.7% had rebleeding versus 11.4% in the non-EACA group (P=0.02; Table 2). There was a significant difference in survival curves between the 2 groups (log-rank P=0.03) and a decreased risk of rebleeding in EACA-treated patients (hazard ratio=0.23; P=0.05; 95% CI, 0.05 to 0.99; Figure 1). There was a nonsignificant 76% relative reduction in mortality directly attributable to rebleeding in the EACA group.

Complications

There was no significant difference in ischemic complications between patient groups (Table 2). There was a significant 8-fold increase in lower-extremity DVTs in EACA-treated versus non-EACA-treated patients but no increased incidence of pulmonary embolism. There was no significant difference in myocardial infarction, ischemia, stunning, or renal failure between cohort groups (data not significant).

Discussion

Despite the high number of poor-grade patients in this study, 52% of them had favorable 3-month outcomes and only 20%



*AF Treatment: EACA or TA

Figure 2. Outcome in patient treated with and without antifibrinolytic agents.

died. Rebleeding was previously thought to be the major cause of morbidity and mortality before aneurysmal surgical treatment, but early intervention has resulted in significant decreases in poor outcome due to rebleeding.¹¹ In this study, only 4% of patients died of rebleeding. Patients in the EACA group had a 7.2% increase in a favorable 3-month outcome and a 76% reduction in mortality directly attributable to decreased rebleeding. In a previous randomized but non-blinded, non-placebo-controlled study, patients treated acutely with tranexamic acid had a 4.3% absolute increase in favorable outcome.² Although there was no significant difference in outcome between cohorts, this study was not adequately powered to detect a significant difference in outcome. If our outcomes are added to this study, 71% (232/327) of patients treated with EACA or tranexamic acid had a favorable outcome versus 62% (265/426) of non-EACA- or nontranexamic acid-treated patients (adjusted odds ratio=1.27; 95% CI, 0.93 to 1.75; $P=0.14$; Figure 2).

Previous studies on rebleeding often did not take into account rebleeding within 24 hours. In our study, 9% of patients had confirmed rebleeding and 86% of bleeds occurred within 3 days. Patients not treated with EACA were 4.2 times more likely to rebleed, and only 1 EACA-treated patient rebled while receiving EACA. Patients did not differ in baseline characteristics, including aneurysm size, which we have previously found to be associated with an increased risk of rebleeding.⁸ Previous studies of acute antifibrinolytic therapy demonstrated similar rebleeding rates.^{2,5}

No EACA-treated patients had a cerebrovascular occlusion due to intravascular thrombosis on angiography. As a cautionary measure, we terminated EACA 4 hours before angiography, despite the risk of rebleeding, because angiography carries a risk of thromboembolism. There was no difference between the 2 cohorts in terms of ischemic complications. Although the risk of arterial occlusion due to thrombosis was not elevated, EACA-treated patients had an 8-fold increase in lower-extremity DVTs. When controlling for patients with a past history of DVTs, there was still a 5-fold increased risk ($P=0.029$). Although there was an increase in venous thrombosis, there was no increased risk of pulmonary embolism. Our results contrast with the majority of investigations of long-term antifibrinolytic treatment, which did not demonstrate an increased rate of DVT or pulmonary embolism.^{4,12,13} This may be because many previous studies did not use regular Doppler ultrasonography.

In this protocol, the number of patients treated with EACA increased over time. This is consistent with previous programs that instituted protocols before indications, efficacy, dosage, and side-effect profiles were clearly defined.^{14,15} There were a number of selection biases inherent to this study. Although there were no significant differences between EACA- and non-EACA-treated patients, there were likely differences between patient characteristics because patients were not randomized. The exact relevance of these differences and their impact on outcome remain unclear and

can likely only be settled by a randomized clinical trial. Patients may have been more likely to receive EACA if they had a larger initial bleed, which increases the risk of rebleeding. Patients eligible for immediate angiography were less likely to receive EACA, because our policy was to stop EACA administration 4 hours before angiography. These patients underwent angiography and surgical intervention earlier. In the non-EACA-treated group, no patient who underwent angiography within 4 hours of admission had rebleeding. Only 1 patient in the EACA group had rebleeding while actually receiving EACA. The other patient in the EACA group who experienced rebleeding received a loading dose at an outside hospital and then had rebleeding after being transferred and before angiography. This patient did not receive a second dose of EACA because he arrived within the 4-hour window for angiography. These biases would overestimate the rate of rebleeding in the EACA-treated patients. Still, there was no significant difference in exposure time between the 2 groups. Patients with acute ECG changes, cardiac troponin elevations, or symptoms of acute thromboembolism were not treated with EACA, which may underestimate the number of complications in EACA-treated patients.

In summary, a policy of acute EACA administration resulted in decreased aneurysm rebleeding without an increase of serious side effects in our series of patients. Therefore, patients without a history of thromboembolism or acute ECG changes, cardiac troponin elevations, or symptoms of thromboembolism may benefit from acute EACA treatment. A large, randomized, placebo-controlled trial is needed to determine whether acute antifibrinolytic therapy should be accepted as the standard of care in all patients.

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