Effect of short-term ϵ -aminocaproic acid treatment on patients undergoing endovascular coil embolization following aneurysmal subarachnoid hemorrhage

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OBJECTIVE Aneurysmal rebleeding before definitive obliteration of the aneurysm is a cause of mortality and morbidity. There are limited data on the role of short-term antifibrinolytic therapy among patients undergoing endovascular intervention.

METHODS All consecutive patients receiving endovascular therapy for their ruptured saccular aneurysm at the authors' institution between 2000 and 2011 were included in this study. These patients underwent endovascular coiling of their aneurysm within 72 hours of admission. In patients receiving ϵ -aminocaproic acid (EACA), the EACA administration was continued until the time of the endovascular procedure. Complications and clinical outcomes of endovascular treatment after aneurysmal subarachnoid hemorrhage (aSAH) were compared between EACA-treated and untreated patients.

RESULTS During the 12-year study period, 341 patients underwent endovascular coiling. Short-term EACA treatment was administered in 146 patients and was withheld in the other 195 patients. EACA treatment did not change the risk of preinterventional rebleeding in this study (OR 0.782, 95% CI 0.176–3.480; $p = 0.747$). Moreover, EACA treatment did not increase the rate of thromboembolic events. On the other hand, patients who received EACA treatment had a significantly longer duration of hospital stay compared with their counterparts who were not treated with EACA (median 19 days, interquartile range [IQR] 12.5–30 days vs median 14 days, IQR 10–23 days; $p < 0.001$). EACA treatment was associated with increased odds of shunt requirement (OR 2.047, 95% CI 1.043–4.018; $p = 0.037$) and decreased odds of developing cardiac complications (OR 0.138, 95% CI 0.031–0.604; $p = 0.009$) and respiratory insufficiency (OR 0.471, 95% CI 0.239–0.926; $p = 0.029$). Short-term EACA treatment did not affect the Glasgow Outcome Scale score at discharge, 6 months, or 1 year following discharge.

CONCLUSIONS In this study, short-term EACA treatment in patients who suffered from aSAH and received endovascular aneurysm repair did not decrease the risk of preinterventional rebleeding or increase the risk of thrombotic events. EACA did not affect outcome. Randomized clinical trials are required to provide robust clinical recommendation on short-term use of EACA.

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KEY WORDS cerebral aneurysm; subarachnoid hemorrhage; ϵ -aminocaproic acid; endovascular; outcome; complication; vascular disorders

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; EACA = ϵ -aminocaproic acid; IQR = interquartile range; RR = risk ratio; TXA = tranexamic acid.

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ANEURYSMAL subarachnoid hemorrhage (aSAH) is a devastating condition with a mortality rate of at least 25%.⁶ Approximately 10% of patients with aSAH die before reaching the hospital. In general, the most important long-term prognostic factors following acute aSAH are the patient's age, quantity of subarachnoid blood detected on the initial CT scan, and clinical condition on admission.^{9,22,23,38}

The mortality risk for patients who reach the hospital is increased by aneurysmal rebleeding and subsequent arterial vasospasm resulting in cerebral ischemia.^{3,6} Current aSAH management focuses on early circulatory exclusion of the ruptured aneurysm and aggressive management of potential secondary complications.^{5,6} Management at centers with experienced neurovascular surgeons, endovascular interventionists, and neurointensive care units has led to a relative improvement in case fatalities over the last 2 decades.^{6,7,24}

Patients with aSAH are at substantial risk of rebleeding, with rehemorrhage rates of 4% within 24 hours, 20% within 2 weeks, and 50% within 6 months after the initial bleed.⁴⁴ Aneurysm repair, therefore, should preferably be performed as soon as logistically possible, generally within 24–72 hours of presentation.⁶ Prior to treatment, anti-fibrinolytic agents such as ϵ -aminocaproic acid (EACA) have been used to prevent rebleeding. Current American Stroke Association guidelines state, "For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short-term (< 72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding."⁶

We previously studied the effect of short-term EACA treatment on aSAH patients before early microsurgical intervention, but there are few data about the role of short-term EACA therapy before endovascular treatment.^{29,30} These data are particularly important in light of the higher baseline thrombotic risks associated with endovascular treatment compared with microsurgical repair³² and the additional potential risk of thrombotic complications posed by antifibrinolytic agents. In this study, we investigated the role of short-term EACA treatment before endovascular coiling of ruptured cerebral aneurysms.

Methods

After obtaining Indiana University Institutional Review Board approval, we collected data for all consecutive patients who were treated endovascularly for ruptured saccular cerebral aneurysms from January 2000 through December 2011 at our institution. The database did not capture time to intervention, so we retrospectively reviewed the patients' charts to calculate this time interval. We could not find the accurate intervention time for 27 patients, yet all patients received endovascular treatment within 72 hours from the time of hospital admission. Clinical outcomes were assessed by independent clinical nurses who did not consistently know about the treatment group assignment at the time of their evaluations.

These patients were divided into 2 groups: those receiving EACA before intervention and those not receiving

EACA. EACA use was based on the consistent preference of the individual vascular neurosurgeon who was on call at the time of the patient's admission. The surgeons who preferred the use of EACA and those who did not were equally and randomly assigned to taking neurovascular call. This fact is likely to introduce some degree of randomization for the administration of EACA. Treated patients received an intravenous loading dose of 5–10 g of EACA followed by a maintenance dose of 2 g/hr until the time of their endovascular procedure.

Data related to demographics, aneurysm characteristics, complications, and outcomes of endovascularly treated aneurysms were retrospectively analyzed. Demographic data included age, race, sex, comorbidities, smoking status, Hunt and Hess score, and Fisher grade on admission.^{9,22,23} Aneurysm characteristics included size, location, and multiplicity. Complications were measured as rebleeding, vasospasm, clinical stroke, radiological infarction, hydrocephalus, need for shunt, cardiac complications, pulmonary edema, respiratory insufficiency, systemic complications, deep venous thrombosis, and death before hospital discharge. The length of hospital stay was also assessed.

Nonparametric variables are expressed as the median with interquartile range (IQR). Continuous variables were compared using the Student t-test and nonparametric variables, using the Mann-Whitney test. Chi-square and Fisher's exact tests were used to compare categorical variables. Multivariate logistic regression was used for assessing the adjusted effect of EACA treatment in the presence of variables that demonstrated a significant association with the use of EACA in the univariate analysis. The results are shown as odds ratios with 95% confidence intervals. Multivariate linear regression was used for assessing the relationship between EACA and length of stay as an outcome, adjusting the effect of aneurysm location, admission grade, and time to intervention.

Patients were evaluated through follow-up examinations at 6 and 12 months following discharge from the hospital. The overall survival analysis was performed using the Cox proportional hazards regression model. Probability values < 0.05 are considered significant.

Results

During the 12-year study period, 341 aSAH patients received endovascular treatment at our institution. Tables 1 and 2 summarize patient characteristics for the studied population. As shown in Table 1, there was no statistically significant demographic difference between the patients who did or did not receive EACA treatment. Aneurysm characteristics (Table 2) differed between the 2 groups: the percentage of posterior circulation aneurysms was higher among the patients receiving EACA ($p = 0.004$). The distribution of the Hunt and Hess grade was also different between the 2 groups. Patients who underwent EACA treatment presented in a worse clinical grade ($p = 0.039$) and harbored more midline aneurysms ($p = 0.002$). Finally, time to intervention was longer in patients receiving EACA ($p < 0.001$). There was no other statistically significant difference in aneurysm characteristics between the groups.

TABLE 1. Baseline characteristics of the studied patients*

Characteristic	Total (n = 341)	No EACA (n = 195)	EACA (n = 146)	p Value
Mean age in yrs ± SD	59.26 ± 14.75	60.27 ± 14.91	57.92 ± 4.49	0.147
Sex				0.301
Female	239 (70.1)	141 (72.3)	98 (67.1)	
Male	102 (29.9)	54 (27.7)	48 (32.9)	
Race				0.847
White	307 (90.0)	175 (89.7)	132 (90.4)	
Black	20 (5.9)	11 (5.6)	9 (6.2)	
Hispanic	7 (2.1)	5 (2.6)	2 (1.4)	
Asian	2 (0.6)	1 (0.5)	1 (0.7)	
Other	4 (1.2)	3 (1.5)	1 (0.7)	
Unknown	1 (0.3)	0 (0)	1 (0.7)	

* Values are reported as the number of patients (%) unless specified otherwise.

Twelve patients (3.5%; 6 patients in each group) suffered from aneurysmal rebleeding before endovascular treatment (Table 3). Symptomatic vasospasm was detected in 17% of the patients, with a trend toward increased vasospasm in the EACA-treated versus untreated patients ($p = 0.072$); significantly more shunts were placed in the patients receiving EACA treatment ($p = 0.004$). Patients receiving EACA required a longer duration of hospital stay than the untreated patients ($p < 0.001$), possibly reflecting their higher Hunt and Hess grade at admission. Clinical stroke and radiographic infarct rates were not statistically different between the 2 groups. Death during hospitalization was not significantly different between the 2 groups in the univariate analysis ($p = 0.460$).

Table 4 shows the multivariate analysis for complications and outcomes while accounting for the differences (location of the aneurysm, Hunt and Hess grade at presentation, and time to intervention) between the 2 groups. EACA treatment did not change the risk of pre-interventional rebleeding in this study (OR 0.782, 95% CI 0.176–3.480; $p = 0.747$). More shunts were placed in the group receiving EACA (OR 2.047, 95% CI 1.043–4.018; $p = 0.037$), but there were fewer cardiac complications (OR 0.138, 95% CI 0.031–0.604; $p = 0.009$) and cases of respiratory insufficiency (OR 0.471, 95% CI 0.239–0.926; $p = 0.029$) in this group. The adjusted odds of death in patients who received EACA were not significantly different from the untreated group (OR 1.152, 95% CI 0.560–2.373; $p = 0.700$). Multivariate analysis of the length of stay demonstrated that administration of the EACA increases the mean length of stay by 4.161 days (SD 1.499 days, $p = 0.006$).

Figure 1 shows the survival analysis performed using the Cox regression model. EACA treatment, aneurysm location, and Hunt and Hess grade at admission were independent variables in the model. The results of analysis show that EACA treatment had a nonsignificant impact on improving survival (adjusted HR 0.998, 95% CI 0.541–1.839; $p = 0.994$).

TABLE 2. Comparison of aneurysm characteristics in the studied patients*

Aneurysm Characteristics	Total (n = 341)	No EACA Treatment (n = 195)	EACA Treatment (n = 146)	p Value
Confirmed aneurysm				0.477
1	255 (74.8)	143 (73.3)	112 (76.7)	
>1	86 (25.2)	52 (26.7)	34 (23.3)	
Location				0.004
Anterior	214 (62.8)	135 (69.2)	79 (54.1)	
Posterior	127 (37.2)	60 (30.8)	67 (45.9)	
Location				0.002
Left	105 (30.8)	67 (34.4)	38 (26.0)	
Right	95 (27.9)	63 (32.3)	32 (21.9)	
Midline	141 (41.3)	65 (33.3)	76 (52.1)	
Size in mm				0.079
Median	7	7	8	
IQR	5–10	5–9	5–10	
Time to intervention in hrs†				<0.001
Median	23	19	28	
IQR	14–44	12–38	16–49	
Hunt & Hess grade				0.039
Median	II	II	III	
IQR	I–IV	I–III	I–IV	
Fisher grade				0.984
Median	3	3	3	
IQR	3–4	3–4	3–4	

* Values represent the number of patients (%) unless indicated otherwise.

Boldface type indicates statistical significance.

† Time to intervention was not available in 27 patients.

Discussion

To contextualize the results of this study, we reviewed the literature on antifibrinolytic therapy for preventing rehemorrhage after aSAH. Since our study is the first that focuses on EACA treatment in patients undergoing endovascular repair, comparisons are inevitably made with the available literature on surgical repair. Rebleeding after aSAH is thought to depend on the equilibrium between coagulation cascades and fibrinolysis in the aneurysmal microenvironment.^{15,31,42} Antifibrinolytic agents, including EACA, tranexamic acid (TXA), and their equivalents, have been investigated in the prevention of preoperative rebleeding. Antifibrinolytic agents function through competitive inhibition of plasminogen activation, preventing the formation of the proteolytic enzyme plasmin and thereby preventing fibrin degradation within the hemostatic plug.²⁹ The role of these agents is not fully established with respect to treatment efficacy and the potential for harm in the form of delayed cerebral ischemia.

Rebleeding Incidence

The use of antifibrinolytic therapy after aSAH was first proposed in 1968 by Mullan and Dawley.³⁴ Based

TABLE 3. Comparison of aSAH complications and outcomes (univariate analysis)*

Complications or Outcome	Total (n = 341)	No EACA (n = 195)	EACA (n = 146)	p Value
Preinterventional rebleeding	12 (3.5)	6 (3.1)	6 (4.1)	0.609
Vasospasm	58 (17.0)	27 (13.8)	31 (21.2)	0.072
Clinical stroke	29 (8.5)	14 (7.2)	15 (10.3)	0.265
Radiological infarction	51 (15.0)	33 (16.9)	18 (12.3)	0.295
Hydrocephalus	130 (38.1)	72 (36.9)	58 (39.7)	0.598
Shunt	49 (14.4)	19 (9.7)	30 (20.5)	0.004
Systemic complications	94 (27.6)	58 (29.7)	36 (24.7)	0.298
Pulmonary embolism	3 (0.9)	1 (0.5)	2 (1.4)	0.577
Deep venous thrombosis	17 (5.0)	10 (5.1)	7 (4.8)	0.970
Cardiac complications	18 (5.3)	15 (7.7)	3 (2.1)	0.027
Pulmonary edema	7 (2.1)	1 (0.5)	6 (4.1)	0.045
Respiratory insufficiency	67 (19.7)	43 (22.1)	24 (16.4)	0.218
Length of stay in days				<0.001
Median	17	14	19	
IQR	10–26	10–23	12.5–30	
Death during hospitalization	46 (13.5)	24 (12.3)	22 (15.1)	0.460
GOS score				
Time of discharge				
Median	4	4	4	
IQR	3–5	3–5	3–5	
6 mos				
Median	5	4	5	
IQR	4–5	4–5	4–5	
1 yr				
Median	5	5	5	
IQR	4–5	4–5	4–5	

* Values represent the number of patients (%) unless indicated otherwise. Boldface type indicates statistical significance.

on the management practice of delayed surgical intervention in that era, antifibrinolytic therapy was used for 2–6 weeks.^{31,34} It demonstrated reduced rebleeding^{11,26,43} but an increased incidence of delayed cerebral ischemia.^{10,27,43}

Over the past 30 years, the trend for the care of ruptured aneurysms has centered on early intervention,²⁹ alleviating the need for prolonged antifibrinolytic therapy. However, there still may be a significant time interval between the onset of hemorrhage and definitive intervention in certain situations, particularly when a patient is transferred to a tertiary care center. During this period, maximizing protection from rebleeding is desirable. The Cochrane database first published a systematic review in 2003, which halted the use of antifibrinolytic therapy due to an overall nonstatistically significant increase in detrimental outcomes from delayed ischemic deficits associated with antifibrinolytic therapy.³⁷ This study was updated in 2013 to include an additional study, thereby including

TABLE 4. Multivariate analysis of aSAH complications and outcomes*

Response Variable	OR (EACA/ no EACA)	95% CI	p Value
Preinterventional rebleeding	0.782	0.176–3.480	0.747
Vasospasm	1.314	0.705–2.446	0.390
Clinical stroke	1.877	0.826–4.264	0.133
Radiological infarction	0.656	0.331–1.297	0.225
Hydrocephalus	0.798	0.472–1.348	0.398
Shunt	2.047	1.043–4.018	0.037
Systemic complications	0.573	0.318–1.032	0.064
Pulmonary embolism	2.119	0.167–26.974	0.563
Deep venous thrombosis	0.848	0.283–2.547	0.770
Cardiac complications	0.138	0.031–0.604	0.009
Pulmonary edema†			
Respiratory insufficiency	0.471	0.239–0.926	0.029
Death during hospitalization	1.152	0.560–2.373	0.700

* Boldface type indicates statistical significance.

† No patient remained in the “No EACA” group after excluding the 27 patients in whom time to intervention was not available.

1904 patients in the systematic review, but all 10 analyzed studies had been published prior to 2002.² Importantly, the antifibrinolytic treatment duration for patients in these studies ranged from less than 72 hours up to 6 weeks, with 9 studies using TXA (4–9 g/day) and 1 study using EACA (24 g/day). Despite its interstudy heterogeneity, this meta-analysis revealed a reduced risk of rehemorrhage (risk ratio [RR] 0.65, 95% CI 0.44–0.97) and an increased risk for cerebral ischemia (RR 1.41, 95% CI 1.04–1.91). The overall results demonstrated no benefit in either mortality or overall outcome.² This lack of disparity in outcomes is thought to represent a balance between the risk of recurrent hemorrhage and the risk of cerebral ischemia.

Our group conducted 2 studies, one with 307 patients and another with 164 patients, to evaluate the utility of a short-term (< 72-hour) high-dose EACA protocol before early microsurgery. The goal of this protocol was to concomitantly decrease the risk for rehemorrhage while avoiding iatrogenic cerebral ischemia. The results of these 2 studies showed a 1.3% and 2.8% incidence of rebleeding and an 8% and 7.4% incidence of delayed cerebral deficits.^{29,30} Our previous studies either included historical controls abstracted from previous reports or did not conduct any comparative statistical analysis.

A 505-patient randomized controlled trial using TXA,¹⁹ a 356-patient retrospective cohort study using EACA, and a 73-patient controlled prospective nonrandomized EACA study,^{17,41} investigated short-term antifibrinolytic therapy. Results of the TXA- and EACA-controlled studies reported significant reduction in the incidence of rebleeding in the treated versus untreated groups: 2.4% versus 10.8%, and 2.7% versus 11.4%, respectively.^{19,41} Both of these studies were included in a meta-analysis that examined 17 studies with a total of 2872 patients and represented the only studies available that investigated short-term anti-fi-

FIG. 1. Survival analysis. Adjusted HR 0.998, 95% CI 0.541–1.839; $p = 0.994$.

brinolytic therapy.¹³ The results of the meta-analysis further supported the benefits of a short-term (< 72 hours) treatment regimen to prevent rebleeding and decrease the risk of poor functional outcome.¹³

As a result of the available data for short-term antifibrinolytic regimen, the American Heart Association/American Stroke Association published its most recent guidelines stating that short-term (< 72 hours) antifibrinolytic therapy, in the absence of contraindications, is a reasonable option in the setting of an unavoidable delay in aneurysm obliteration during the interim between clinical presentation and definitive aneurysm repair.⁶ Additional short-term treatment data will be needed to reliably assess the validity of the American Heart Association/American Stroke Association guidelines for modern aSAH management. The previous systematic review by Baharoglu et al. in 2013 on antifibrinolytic therapy for aSAH included only one study analyzing antifibrinolysis with a duration of less than 72 hours, and these studies did not routinely use hypervolemic therapy or calcium channel blockers.²

Uniquely, the results of our current study indicate that EACA was not associated with a diminished rate of pre-interventional rebleeding in the multivariate analysis for the patients receiving endovascular coiling, 3.1% and 4.1% for EACA-treated and untreated cohorts, respectively (OR 0.782, 95% CI 0.176–3.480). This is not consistent with the previous studies at our institution or the others that we have reviewed, keeping in mind that these studies refer to the patients who underwent microsurgery.^{17,19,29,30,41}

In our study, multiple variables may have accounted for the lack of efficacy of EACA in decreasing the risk of rebleeding. At our institution, the time from aneurysm rupture to intervention has progressively decreased in the recent years between our current and prior studies. Unfortunately, despite our efforts, we were unable to accurately assess the time of initial hemorrhage to definitive treatment in our patients to objectively measure the effect of this parameter on the current results and compare the

findings with our previous studies. Some of our patients were transferred from outside institutions and therefore the exact time from ictus to treatment remains unknown. There is also a notable variation in the literature regarding rebleeding rates for the groups assigned to early intervention. A literature review by Starke and Connolly reported that the likely percentage of rebleed rates is between 5.3% and 11.4%, with most rebleeds occurring within 6 hours of the initial hemorrhage.⁴⁰

A more recent study of 293 patients confirmed rebleed rates of 12% with an additional 4% having possible rebleeds within a median time from initial hemorrhage to rebleed of 3 hours.¹⁴ A progressive decrease in the time from diagnosis until intervention is likely to be different for the patients in the endovascular and microsurgical group, similar to the findings in the ISAT (International Subarachnoid Aneurysm Trial) and BRAT (Barrow Ruptured Aneurysm Trial) studies.^{31,33} This can potentially explain the lack of reduction in the rehemorrhage rates in our cohort promptly treated via endovascular coiling. This phenomenon emphasizes an important point about evaluation of antifibrinolytic efficacy research—when comparing study results for rebleed rates and outcome scores, the variable of endovascular versus microsurgical intervention can confound comparison analysis. Unfortunately, a reliable assessment of time of initial hemorrhage to treatment can be problematic because of the high number of patients undergoing interhospital transfers. The type of antifibrinolytic agent used is another important variable to consider when comparing study results.

Differences in Antifibrinolytic Agents

Although EACA was used in our institution's previous studies, this antifibrinolytic agent was used in only 1 of the 10 studies included in the Cochrane systematic review.² The other 9 studies in that review used TXA. This difference may have contributed to differing results with respect to the prevention of rebleeding. TXA and EACA differ in plasminogen/plasmin binding affinity; TXA has 6–10 times greater affinity.⁸ However, placebo-controlled studies during cardiac surgery have demonstrated comparable efficacy in antifibrinolytic activity between TXA and EACA.^{16,20}

Antifibrinolytic Agent Dosing and Thrombotic Risk

Historically, studies found in the literature described a 24- to 48-hour delay in the onset of EACA effectiveness,^{4,12,26} which was later attributed to the lack of a loading dose.^{27,36} Our study in 1997 monitored serum levels of EACA. We found that therapeutic levels were achieved within 24 hours through a bolus dose followed by subsequent continuous intravenous infusion.³⁰ Starke et al. used a 4-g loading dose with a 1-g/hr maintenance infusion and demonstrated a beneficial impact on rebleeding rates.⁴¹ The dosage regimen used in our study (a 5- to 10-g bolus dose with subsequent 2-g/hr infusion) should allow for similar therapeutic efficacy. Our institution's treatment regimen differs slightly from those of other centers in that an antifibrinolytic agent (EACA) is routinely infused until the patient is transported to the procedure

or occasionally until the aneurysm is excluded via coil embolization. This is in contrast to the routine at other institutions, which stop antifibrinolytic treatment at least 4 hours prior to the procedure because of the perceived thrombotic risk.^{17,41}

Aneurysmal SAH potentially creates a prothrombotic and proinflammatory state as indicated by serum markers, such as platelet count, leukocyte count, erythrocyte sedimentation rate, and C-reactive protein levels.²⁵ In addition, thrombotic risks are reported to be higher with endovascular treatment compared with microsurgery.^{32,35} There is a concern that the combination of antifibrinolytic treatment in the setting of endovascular coiling and aSAH could potentiate thrombotic risk. In a retrospective study of 83 patients, with short-term (< 72 hours) EACA therapy in angiographically negative SAH, Hui et al. reported no increase in thrombotic complications, including deep venous thrombosis ($p = 0.65$), pulmonary embolism ($p = 1.0$), delayed cerebral ischemia ($p = 1.0$), and myocardial infarction ($p = 1.0$).²¹ This supports a benign adverse thromboembolic effect profile for short-term EACA use for prevention of rebleeding. However, a nonrandomized prospective controlled study by Starke et al. demonstrated an 8-fold increased risk of deep venous thrombosis with a similar short-term EACA regimen, but the authors failed to show an increased risk for pulmonary embolism or delayed cerebral ischemia.⁴¹

Long-Term Outcomes

Despite the potential efficacy of antifibrinolytic therapy in reducing the risk of rebleeding, the studies on short-term administration of the drug have not demonstrated a statistically significant long-term clinical benefit.^{2,17,19,21,39,41} This is consistent with our findings. However, a pooled analysis by Starke et al.⁴¹ with study data from Hillman et al.¹⁹ showed a 9% increase in favorable 3-month modified Rankin Scale score (0–3). Earlier studies on prolonged use of antifibrinolytic agents suggested that an increase in risk of delayed cerebral ischemia offsets the benefits from reduction in the rate of rebleeding;² however, in our study, neither the risk of rebleeding nor ischemia was significantly different between the 2 groups. Similar recent studies investigating short-term antifibrinolytic therapy have also failed to demonstrate a statistically significant increased risk of ischemia compared with controls.^{19,21,39,41} Therefore, the idea that the lack of improved outcomes with antifibrinolytic therapy is explained by an increased rate of ischemia is not supported by recent studies involving short-term antifibrinolytic therapy. To determine the efficacy of antifibrinolytic therapy in improving long-term outcomes, additional randomized controlled trials are required.

Length of Stay

Our data indicate that the median length of hospital stay for the EACA-treated patients was significantly longer than that for the control patients, 19 days and 14 days, respectively ($p < 0.001$). This difference is not likely related to EACA treatment, but rather correlates with the degree of asymmetry in clinical condition between the groups, with the EACA group including patients who presented in a worse clinical status.

Hydrocephalus Incidence

Chronic hydrocephalus is a known sequela of aSAH, with rates ranging from 20% to 63.4%^{18,28} and risk factors including aneurysm location and volume of hemorrhage.¹ In our study, the rates for ventricular shunt placement in the EACA versus no-EACA cohorts were 20.5% and 9.7% ($p = 0.004$), respectively.

The Cochrane systematic review of 10 studies included 5 that reported the incidence of hydrocephalus, all of which used longer courses of antifibrinolytic agents (> 72 hours).² Compilation of this data determined that antifibrinolytic use was not associated with an increase the incidence of hydrocephalus (RR 1.11, 95% CI 0.90–1.36).² Harrigan et al. found no statistical difference in the incidence of either ventriculostomy or shunt placement when comparing microsurgical and endovascular intervention for patients with aSAH.¹⁷ The data from our study, which exclusively evaluated an endovascularly treated population, demonstrated a significant correlation between EACA treatment and placement of a shunt but not the overall incidence of hydrocephalus. It should be noted that the EACA group had a higher incidence of midline aneurysms and a higher initial Hunt and Hess score, which may also have contributed to the need for a shunt. Also, we did not specifically review the incidence of intraventricular hemorrhage in this group due to the unavailability of the data.

Limitations

This study is primarily limited by being a retrospective cohort from a single institution. We tried to partially overcome this limitation by expanding the study over a 12-year period, yet prospective multicenter studies would eliminate this limitation and increase the patient sample size. The relatively small sample size in this study may overlook the small differences in the rate of preintervention rebleeding. Finally, since the patients were not randomly assigned to treated and untreated groups, there is the possibility of selection bias. All of these limitations would be ideally addressed in well-designed prospective multicenter studies.

Conclusions

To our knowledge, this is the first study that specifically assesses short-term EACA use in aSAH patients undergoing endovascular treatment. We were unable to detect a significant difference in the risk of cerebral ischemia related to the use of EACA. However, we also did not detect a difference in preintervention rehemorrhage rates. To better define the role of EACA in aSAH and to develop a robust clinical guideline for the use of antifibrinolytic therapies, a randomized placebo-controlled trial is necessary.

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Disclosures

Dr. Shah reports that he is a consultant for Stryker.

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Conception and design: Cohen-Gadol, Malekpour, Bohnstedt, Radmand, Sethia, Hendricks, Leipzig, Payner, Shah, Scott, DeNardo. Acquisition of data: Cohen-Gadol, Malekpour, Kulwin, Radmand, Sethia, Hendricks, Leipzig, Payner, Shah, Scott, DeNardo, Sahlein. Analysis and interpretation of data: all authors. Drafting the article: Cohen-Gadol, Malekpour, Bohnstedt, Radmand, Sethia, Mendenhall, Weyhenmeyer, Hendricks, Leipzig, Payner, Shah, Scott, DeNardo, Sahlein. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Cohen-Gadol. Statistical analysis: Cohen-Gadol, Malekpour, Radmand, Sethia, Mendenhall, Weyhenmeyer, Hendricks, Scott, DeNardo, Sahlein. Administrative/technical/material support: Cohen-Gadol, Malekpour, Mendenhall, Weyhenmeyer, Leipzig, DeNardo. Study supervision: Cohen-Gadol, Malekpour.

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