Clinical Neurology and Neurosurgery 139 (2015) 66–69

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Antifibrinolytic therapy in aneurysmal subarachnoid hemorrhage increases the risk for deep venous thrombosis: A case–control study

Paul M. Foreman[a,*], Michelle Chua[b], Mark R. Harrigan[a], Winfield S. Fisher 3rd[a], R. Shane Tubbs[c], Mohammadali M. Shoja[c], Christoph J. Griessenauer[a]

[a] Department of Neurosurgery, University of Alabama at Birmingham, United States
[b] Harvard Medical School, Harvard University, United States
[c] Children's of Alabama, Birmingham, AL, United States

ARTICLE INFO

Article history:
Received 8 August 2015
Received in revised form 29 August 2015
Accepted 8 September 2015
Available online 10 September 2015

Keywords:
Aneurysmal subarachnoid hemorrhage
Antifibrinolytic
ε-Aminocaproic acid
Deep venous thrombosis

ABSTRACT

Objectives: Aneurysm re-rupture is associated with significant morbidity and mortality in aneurysmal subarachnoid hemorrhage (aSAH). While antifibrinolytics reduce aneurysm re-rupture rates, they have been associated with hydrocephalus, delayed cerebral ischemia, and venous thrombosis. We performed a case–control study in patients enrolled in the Cerebral Aneurysm Renin Angiotensin System (CARAS) study to evaluate the impact of short course (<48 h) ε-aminocaproic acid (EACA) on deep venous thrombosis (DVT) rates.

Patients and methods: A case–control study design was utilized to evaluate the effect of EACA on DVT formation. All cases and controls were obtained from the CARAS study, a prospective, blinded study assessing the association of polymorphisms in the renin angiotensin system and aSAH.

Results: One hundred and twenty-eight eligible patients were enrolled in CARAS. Overall, 48 (37.5%) patients were screened for DVT, 57 (44.5%) patients were treated with short course (<48 h) EACA, and 8 (6.3%) patients suffered a re-rupture (4 treated with EACA). Ten patients (7.8%) were diagnosed with DVT as evidenced by Doppler US and represent the cases. Twenty controls without evidence of a DVT matched for age, sex, race, tobacco history, Hunt–Hess score, Fisher grade, body mass index, and length of stay were identified from the remaining pool of 118 patients. EACA was found to significantly increase the risk of DVT formation in patients with aSAH (OR 8.49, CI 1.27–77.1).

Conclusion: Short course (<48 h) administration of EACA in patients with aneurysmal subarachnoid hemorrhage is associated with an 8.5 times greater risk of DVT formation.

1. Objectives

Aneurysmal subarachnoid hemorrhage (aSAH) is a unique form of hemorrhagic stroke caused by rupture of an intracranial aneurysm with an estimated incidence of 10 per 100,000 person-years [1]. Aneurysm re-rupture prior to treatment represents a major source of early morbidity and carries a mortality rate of up to 51% [2]. Efforts to reduce the likelihood of early re-rupture have focused on early intervention for treatment of the aneurysm and administration of antifibrinolytics. Early intervention, either through surgical clipping or endovascular embolization, has proven effective in reducing rates of re-rupture and represents a Class I recommendation in the AHA/ASA Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage [3]. While antifibrinolytics have demonstrated efficacy in reducing re-rupture rates, concerns that antifibrinolytics increase the risk of hydrocephalus, delayed cerebral ischemia, and venous thrombosis have limited widespread acceptance [4–8].

Deep venous thrombosis (DVT) complicates nearly 20% of cases of aSAH and poses a particularly difficult clinical challenge [9]. The risks and benefits of anticoagulation in this setting are complex and inconclusive, and thus primary prevention remains the treatment of choice. Despite seemingly evident thrombotic risk posed by antifibrinolytic medications, data regarding antifibrinolytics as a risk factor for DVT in patients with subarachnoid hemorrhage (SAH) is mixed [5,10–12]. Contemporary investigation of short course ε-aminocaproic acid's affect on DVT risk in non-aneurysmal SAH

* Corresponding author at: Faculty Office Tower 1005, 510 20th Street South, Birmingham, AL 35294, United States.
E-mail address: pforeman@uabmc.edu (P.M. Foreman).

http://dx.doi.org/10.1016/j.clineuro.2015.09.005
0303-8467/

patients [11] and aneurysmal SAH patients [5] have reached different conclusions.

We present a case–control study of prospectively gathered aSAH patients to evaluate the impact of short course (<48 h) ε-aminocaproic acid (EACA) on DVT rates.

2. Patients and methods

A case–control study design was utilized to evaluate the effect of EACA on DVT formation. All cases and controls were obtained from the CARAS (Cerebral Aneurysm Renin Angiotensin System) study, a prospective, blinded study designed to evaluate associations between the common genetic polymorphisms in the renin angiotensin system and occurrence and rupture of cerebral aneurysms, development of cerebral vasospasm and delayed cerebral ischemia, and outcome in aSAH. All aSAH were eligible for inclusion. CARAS consists of a one time blood draw, performed with routine laboratory testing, and the collection of clinical data. It does not carry any implication for patient management and therefore should not influence DVT rates. The study was started in December 2012 and completed enrollment in February 2015 with final results expected to be published later this year.

2.1. Patients

All patients presenting to the University of Alabama at Birmingham with aSAH were screened for inclusion in CARAS study. The diagnosis of SAH was established on the basis of the admission CT scan or xanthochromia of cerebrospinal fluid (CSF). A ruptured cerebral aneurysm was confirmed by CT angiography (CTA) or digital subtraction angiography (DSA). Exclusion criteria included age < 19 years and any associated genetic disease/syndrome that could account for the presence of an intracranial aneurysm (i.e. polycystic kidney disease, Turner syndrome, Noonan syndrome, Ehler–Danlos syndrome type 4, Marfan syndrome neurofibromatosis type 1), as well as systemic diseases (i.e. congestive heart failure, cirrhosis, etc.) that could affect with the renin–angiotensin system.

Presence of a DVT was a secondary outcome measure in the CARAS study and all data was collected in a prospective manner. Data pertinent to this study includes: age, sex, race, tobacco history, Hunt–Hess score, Fisher grade, aneurysm re-rupture, body mass index (BMI), length of stay (LOS), EACA use, Doppler ultrasound (US) screening, and presence of DVT.

Matching was performed with a 2:1 (control:case) ratio. Cases consisted of aSAH patients diagnosed with a DVT and controls included aSAH patients without a diagnosis of DVT. A patient did not need to undergo a negative screening test for a DVT to be included as a control. If they were not diagnosed with a DVT, they were assumed to not harbor a DVT and thus were eligible for use as a control. Cases and controls were matched for age, sex, race, tobacco history, Hunt–Hess score, Fisher grade, BMI, and LOS. The impact of EACA with regard to DVT diagnosis was investigated.

2.2. Management

Patients presenting with aSAH were treated in accordance with contemporary standards of care consisting of: ICU monitoring, treatment of hydrocephalus, early (<24 h when clinically feasible) intervention for aneurysm treatment, oral nimodipine, maintenance of euvolemia, compression stockings, and sequential compression devices. Of note, no patient received prophylactic anticoagulation for DVT.

The use of EACA was used at the discretion of the treating cerebrovascular attending. Patients are not routinely screened with electrocardiograms (EKG), cardiac enzymes, or lower-extremity ultrasound (US) prior to initiation of EACA. A history of DVT or other hypercoagulable state is viewed as a relative contraindication, not absolute, and would be discussed with the cerebrovascular and critical care attendings prior to initiation of EACA. After confirmation of aSAH, patients are given EACA as a 5 g bolus followed by 1 g/h for a maximum duration of 48 h.

2.3. Diagnosis and screening

Doppler ultrasonography was used for screening and diagnosis of deep venous thrombosis of both the upper and lower extremities. Doppler US is a non-invasive imaging modality performed at the bedside by a formally trained US technician. Complete vein compressibility rules out the presence of a DVT where as lack of compressibility is indicative of a DVT. Direct visualization of the blood clot, loss of augmentation, or Doppler flow abnormalities may also indicate presence of a DVT. Doppler US was interpreted and reported by an attending radiologist blind to the use of EACA. Screening Doppler US was obtained on grounds of clinical suspicion including but not limited to extremity swelling, extremity pain, extremity erythema, unexplained fever, unexplained leukocytosis, and unexplained shortness of breath.

2.4. Statistics

Categorical variables were compared between groups by Fisher's exact test. Numerical variables were compared between groups by the Mann–Whitney–Wilcoxon test. Statistical significance was assessed at $p < 0.05$. A maximum likelihood estimate of the odds ratio was calculated, with a computation of the 95% confidence interval using R version 3.1.1 (http://www.r-project.org).

3. Results

3.1. Patients

One hundred and twenty-eight consecutive patients with aSAH were enrolled in the CARAS study at the University of Alabama at Birmingham. Overall, 48 (37.5%) patients were screened for DVT with Doppler US, 57 (44.5%) patients were treated with short course (<48 h) EACA, 20 of the 57 (35.1%) patients treated with EACA were screened, 28 of the 71 (39.4%) patients not treated with EACA were screened, 20 of the 48 (41.7%) who were screened were treated with EACA, and 8 (6.3%) patients suffered a re-rupture (4 were treated with EACA). Ten patients (7.8%), average age of 53.6 years, were diagnosed with DVT as evidenced by Doppler US and represent the cases. Seven of the 10 (70%) were treated with EACA and 3 (30%) were not. No patient experienced a pulmonary embolism (PE). Twenty matched controls without the diagnosis of a DVT, average age 56.4 years, were identified from the remaining pool of 118 patients. Demographics including age, sex, race, tobacco history, Hunt–Hess score, Fisher grade, BMI, and LOS are presented in Table 1. There were no significant differences between groups with regard to these data points; however, rate of screening was significantly higher among the cases.

3.2. ε-Aminocaproic acid and DVT

EACA was found to be associated with a significantly increased risk of DVT formation in patients with aSAH (OR 8.49, CI 1.27–77.1) (Table 2).

3.3. Craniotomy and DVT

Craniotomy was found to be associated with a significantly increased risk of DVT formation in patients with aSAH (OR 12.4, CI 1.29–637.2) (Table 2). However, there was not a statistically