Aneurysmal subarachnoid hemorrhage (aSAH) is a rare, devastating cause of stroke that carries a case fatality rate of up to 67%. With improvements in aSAH treatment and ICU care, more patients who have experienced aSAH are surviving the initial event. Long-term cognitive impairment occurs in up to 70% of patients surviving the initial hemorrhage. Cognitive impairments often co-manifest with life-changing psychosocial problems, with 59% of surviving patients unable to return to their previous occupation, and up to 93% demonstrating...
ing deficits in activities of daily living. Verbal memory, visual memory, language, and executive function are the most commonly impaired cognitive domains. Although aSAH-related cognitive dysfunction may improve over time, most patients report lifelong cognitive deficits.

Additional brain injury occurring after the initial hemorrhage may be due to cerebral vasospasm, inflammation, nonobstructive hydrocephalus, microthrombi, cortical spreading depolarization, and neuronal cell death. Specifically, microthrombi and intraparenchymal vasoconstriction have been associated with increased expression of membrane P-Selectin and decreased nitric oxide (NO), as well as ensuing adjacent neuronal apoptosis. Collectively, these pathologic processes result in delayed neurological deficits (DND). Cognitive dysfunction after aSAH is arguably one of the most critical manifestations of DND.

Subarachnoid hemorrhage induces a significant inflammatory response involving numerous cytokines, chemokines, complement, leukocytes, and microglia. The systemic inflammatory response has been demonstrated to correlate with cerebral vasospasm. Additionally, long-term cognitive dysfunction may also be significantly related to neuroinflammation. Inflammatory responses of the same sort result in similar patterns of cognitive dysfunction in diseases as varied as Alzheimer’s disease, HIV infection, traumatic brain injury, and normal aging.

Recent studies have shown the potential benefit of unfractionated heparin in antagonizing mechanisms responsible for DND associated with aSAH. Unfractionated heparin is a mixture of glycosaminoglycans of variable lengths and molecular weights ranging from 3 to 30 kD. As the most negatively charged biological molecule known, heparin has a strong ability to interfere with the functioning of positively charged molecules. Due to the difference in charges, heparin has been demonstrated to interact with over 100 proteins. Interleukins, cytokines, and receptors located on endothelial cells, which are involved in the acute phase response, are positively charged, and thus are a reasonable target for the modulating effects of heparin. Heparin has strong antiinflammatory effects with many possible mechanisms, including binding to cell-surface glycosaminoglycans, preventing leukocyte migration, direct binding to chemokines and cytokines, and inhibition of intracellular NF-kB. Heparin is also able to modulate endothelin-1 (ET-1) activity as well as scavenge free radicals, in addition to upregulation of superoxide dismutase. Significant vasoconstriction due to ET-1 is mediated in vascular smooth muscle cells through the epidermal growth factor receptor (EGFR). Heparin-binding epidermal growth factor, a ligand of EGFR, modulates its transactivation. Low-dose intravenous heparin (LDIVH) provides anticoagulation effects, which may counter the effects of aSAH-induced microthrombi, in addition to all the antiinflammatory effects of heparin. Preclinical studies have demonstrated that neuroinflammation after aSAH can be attenuated through the use of LDIVH, resulting in lessened tissue injury and decreased transsynaptic apoptosis.

Given the report that unfractionated heparin reduces symptomatic cerebral vasospasm and vasospasm-related infarctions, we evaluated its effects on cognitive outcomes. The Montreal Cognitive Assessment (MoCA) is an alternative assessment to the Mini–Mental State Examination (MMSE) and, according to the National Institute of Neurological Disorders, is currently considered the gold standard for rapid cognitive screening in the setting of stroke. Studies have demonstrated that MoCA testing is more sensitive than MMSE in detecting cognitive dysfunction following aSAH. Given MoCA’s emphasis on language, memory, and visuospatial functioning, it is a highly sensitive and effective assessment tool for identifying even mild cognitive impairment.

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In the present study, we evaluated cognitive outcomes in patients with aSAH treated with standard therapy compared with those treated with LDIVH.

Methods

With approval from the institutional review board of the East Carolina University Brody School of Medicine and Vidant Medical Center, we reviewed the records of all patients with aSAH treated by clipping or coiling by a single cerebrovascular neurosurgeon (R.F.J.) between July 2009 and April 2014. Baseline evaluations included CT, vascular imaging, and determination of Fisher grade and World Federation of Neurological Societies (WFNS) grade. All patients were treated according to the American Heart Association’s Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage, with an emphasis on prompt aneurysm obliteration, drainage of cerebrospinal fluid for treatment of hydrocephalus, and maintenance of euvolemia. Patients were treated with 60 mg of oral nimodipine every 4 hours beginning within 48 hours of the ictus, in accordance with the American Heart Association guidelines. Radiographic studies, such as CT, CT angiography (CTA), digital subtraction angiography (DSA), and/or MR angiography (MRA) were routinely performed within 24 hours of treatment to confirm obliteration of the aneurysm, rule out any complication of treatment, and evaluate for the development of hydrocephalus.

In 2012 we began routinely treating patients with secure aSAH with an LDIVH protocol as a new addition to our previous standard of care. The control group included patients receiving the standard of care treatment prior to implementation of the new LDIVH standard of care protocol. The treatment group included patients receiving the newly established LDIVH protocol in addition to the previous standard of care therapy. No patients prior to 2012 were treated with the LDIVH protocol. Concurrently in 2012, it became our standard of care to perform cognitive screening on aSAH patients at 90 days after hemorrhage or longer. Blinded nonstudy personnel, who were unaware of inpatient heparin treatment protocols, administered MoCA testing to all aSAH patients during routinely scheduled follow-up visits, at least 3 months after surgery. Of all aSAH patients treated between July 2009
and April 2014, only those patients who had routine cognitive screening with MoCA testing at least 90 days after the SAH were included in this analysis. We excluded patients from LDIVH treatment if they were deemed to be at a higher risk for hemorrhagic sequelae, namely, presence of a significant tract hemorrhage following ventriculostomy catheter placement; significant contusion following surgical clipping; angiogram-negative SAH; fusiform, mycotic, or blister aneurysms; unsecured aneurysms; patients who had received heparin in the 100 days prior to admission; and delayed presentation.

In the treatment group, patients received LDIVH (10–12 U/kg/hr for approximately 14 days; FDA off-label) beginning 12 hours after aneurysm treatment and continuing until day 14 following the ictus, with activated partial thromboplastin time routinely monitored to ensure that significant anticoagulation was not reached. Of a total of 47 aSAH patients included in the study during this time period, 22 received conventional management and had MoCA scores available, and 25 received LDIVH treatment and had MoCA scores available. In a few cases, more than one MoCA score was available, in which case the most recent score was used.

Statistical Analysis

Descriptive statistics such as frequency and proportion for any discrete variable and mean and standard deviation for any continuous variable are reported. Associations between discrete groups were compared using a chi-square test or Fisher’s exact test. Two-group means were compared using a 2-sample t-test. The mean MoCA scores were compared using a 1-tailed t-test for unequal variance. Statistical significance was determined as \( p < 0.05 \). Linear regression analysis of MoCA scores was performed for multiple potential factors and predictors. Significant factors were simultaneously controlled for using a multivariable linear regression analysis. The data were analyzed using SAS statistical software (version 3.0, SAS Institute).

Results

A total of 47 patients with aSAH were included in the study: 22 patients were treated with standard therapy and 25 were treated with LDIVH. Baseline characteristics demonstrated no statistically significant differences in age, dementia history, sex, Fisher grade, WFNS grade, or number of anterior circulation aneurysms between the control and heparin-treated groups (Table 1).

![Table 1: Baseline patient characteristics](image)

Values are presented as the number of patients unless stated otherwise.

* Chi-square or Fisher’s exact where appropriate for frequency comparisons; two-tailed independent Student’s t-test for continuous variables.

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Scale (mRS) score between the groups, with a mean score of 1.4 ± 0.8 in the control group compared with 1.1 ± 0.8 in the LDIVH group (p = 0.25). Time from aneurysm rupture to MoCA assessment at follow-up was significantly different between the two groups (p < 0.001). Patients treated with heparin had a mean time to follow-up of 7.1 ± 7.4 months compared with 25.4 ± 12.6 months in the control group. There were no hemorrhagic complications or any cases of type II heparin-induced thrombocytopenia.

Linear regression analysis of factors related to the distribution of MoCA scores demonstrated that only LDIVH treatment was associated with a positive influence on MoCA scores ($b = 3.68$, $p = 0.017$; Table 3). Anterior communicating artery aneurysm location and multiple fevers were negatively associated with MoCA scores ($b = -4.85$, $p = 0.003$ [ACoA]; $b = -6.27$, $p = 0.006$ [multiple fevers]). A Fisher grade of 3, vasospasm-related infarct, and WFNS grade ≥ IV did not demonstrate significant correlation with poor MoCA score. Following multivariable linear regression analysis, LDIVH remained positively associated with improved MoCA scores ($p = 0.019$); ACoA aneurysm location ($p = 0.001$) and fevers ($p = 0.0001$) also remained significant negative correlates with cognitive scores. No treatment complications occurred in either group. LDIVH treatment did not result in significant anticoagulation.

**Discussion**

Early treatment of aneurysms, the development of treatment protocols, and the development of neurocritical care as a unique specialty together have led to tremendous improvements in overall morbidity and mortality for aSAH patients. However, long-term cognitive dysfunction, often discovered in the months following aSAH, has emerged as a newly recognized delayed sequela. To date, no study has shown any treatment that improves cognitive outcome after aSAH. Our preliminary study suggests that the use of LDIVH prophylaxis, in addition to standard therapy, may safely reduce the incidence of cognitive dysfunction experienced by patients after aSAH compared with those treated with standard therapy alone. Our study builds on a previous study by Simard et al., which provided self-
reported cognitive outcomes rather than formal cognitive testing. Two previous randomized trials evaluated low-molecular-weight heparin in aSAH with conflicting results regarding vasospasm, although they did not evaluate cognitive outcomes. The current study and the study by Simard et al. differ from the aforementioned studies in that a continuous infusion of unfractionated heparin was administered, rather than scheduled subcutaneous injections of low-molecular-weight heparin. It is possible that either the route or the schedule of administration or the type of heparin may influence results.

Both the occurrence and the severity of fever have been well documented as negative predictive factors of neurological outcomes in aSAH. One prospective study evaluating 353 patients demonstrated that patients with an mRS score of 4–6 demonstrated a mean maximum temperature of 0.7 °C higher than those with an mRS score of 0–3. While the etiology of thermoregulatory dysfunction is based on animal models after acute brain injury, it is believed to be a result of delayed neurological insults affecting the hypothalamus, midbrain, or pons. In our study, fever was negatively correlated with worse MoCA scores in both treatment groups, consistent with prior reports.

ACoA aneurysms are a significant independent risk factor for the development of cognitive dysfunction after aSAH. Kreiter et al. evaluated 113 patients with ACoA aneurysms with neuropsychological testing at a mean interval of 107 ± 21 days. The results demonstrated that non-posterior circulation aneurysms were independent predictors of abnormal visual memory and verbal memory. More recently, a significant number of studies evaluated the incidence of adverse cognitive outcomes in patients with ACoA aneurysms compared with other locations and were unable to demonstrate this correlation. Manning et al. showed that patients with ACoA aneurysms performed better on the Tower of London executive function test than patients whose ruptured aneurysm was in other locations.

It is important to note that there was significant variability in the time to follow-up examination, which can easily confound correlations. This is evident in the study by Ogden et al., where patient follow-up evaluations ranged from 7 to 115 months after craniotomy. Variability in the testing could potentially mask true differences in cognition between the various aneurysm locations due to the possibility of natural temporal improvement. In our study, there were 10 patients with ACoA aneurysms in the control group and 5 in the LDIVH treatment group (p = 0.12), and ACoA aneurysm location was one of the factors that emerged in our multivariable linear regression analysis.

### Table 3. Linear regression for factors related to the distribution of MoCA scores

<table>
<thead>
<tr>
<th>Factor</th>
<th>β</th>
<th>SE (β)</th>
<th>Univariate p Value</th>
<th>R²</th>
<th>Multivariable p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>2.90</td>
<td>1.71</td>
<td>0.097</td>
<td>0.0601</td>
<td></td>
</tr>
<tr>
<td>Heparin treatment group</td>
<td>3.68</td>
<td>1.49</td>
<td>0.017</td>
<td>0.1005</td>
<td>0.019</td>
</tr>
<tr>
<td>Imaging vasospasm</td>
<td>-0.11</td>
<td>0.95</td>
<td>0.91</td>
<td>0.0044</td>
<td></td>
</tr>
<tr>
<td>Educational level &gt;12 yrs</td>
<td>3.64</td>
<td>2.64</td>
<td>0.183</td>
<td>0.0870</td>
<td></td>
</tr>
<tr>
<td>Fisher grade 3</td>
<td>1.11</td>
<td>1.57</td>
<td>0.49</td>
<td>0.0109</td>
<td></td>
</tr>
<tr>
<td>Vasospasm-related infarct</td>
<td>-3.03</td>
<td>3.18</td>
<td>0.35</td>
<td>0.0260</td>
<td></td>
</tr>
<tr>
<td>WFNS grade ≥IV</td>
<td>-1.93</td>
<td>2.20</td>
<td>0.39</td>
<td>0.0167</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>-1.80</td>
<td>1.67</td>
<td>0.29</td>
<td>0.0252</td>
<td></td>
</tr>
<tr>
<td>Premorbid dysfunction</td>
<td>2.17</td>
<td>3.21</td>
<td>0.50</td>
<td>0.0100</td>
<td></td>
</tr>
<tr>
<td>Discharge to rehab</td>
<td>-3.44</td>
<td>1.79</td>
<td>0.061</td>
<td>0.0758</td>
<td></td>
</tr>
<tr>
<td>Coiling treatment</td>
<td>-0.74</td>
<td>2.10</td>
<td>0.73</td>
<td>0.0027</td>
<td></td>
</tr>
<tr>
<td>Posterior circulation aneurysm</td>
<td>2.64</td>
<td>2.53</td>
<td>0.31</td>
<td>0.0237</td>
<td></td>
</tr>
<tr>
<td>ACoA aneurysm</td>
<td>-4.85</td>
<td>1.53</td>
<td>0.003</td>
<td>0.1825</td>
<td>0.001</td>
</tr>
<tr>
<td>Ventricular drainage</td>
<td>-1.13</td>
<td>1.69</td>
<td>0.50</td>
<td>0.0099</td>
<td></td>
</tr>
<tr>
<td>CSF shunt procedure</td>
<td>0.59</td>
<td>2.10</td>
<td>0.78</td>
<td>0.0017</td>
<td></td>
</tr>
<tr>
<td>Chemical DVT prophylaxis</td>
<td>0.94</td>
<td>1.58</td>
<td>0.55</td>
<td>0.0078</td>
<td></td>
</tr>
<tr>
<td>Any fever (&gt;101.6°F)*</td>
<td>-6.04</td>
<td>1.90</td>
<td>0.003</td>
<td>0.1837</td>
<td></td>
</tr>
<tr>
<td>Multiple fevers</td>
<td>-6.27</td>
<td>2.17</td>
<td>0.006</td>
<td>0.1561</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Isolated fever</td>
<td>-3.80</td>
<td>3.87</td>
<td>0.33</td>
<td>0.0210</td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>-1.81</td>
<td>3.22</td>
<td>0.58</td>
<td>0.0070</td>
<td></td>
</tr>
<tr>
<td>Continuous predictors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>-0.03</td>
<td>0.07</td>
<td>0.64</td>
<td>0.0049</td>
<td></td>
</tr>
<tr>
<td>Length of stay</td>
<td>-0.17</td>
<td>0.12</td>
<td>0.80</td>
<td>0.0014</td>
<td></td>
</tr>
</tbody>
</table>

SE = standard error.

When β is positive and statistically significant, the factor can be considered to positively influence MoCA score distribution. The reverse is true when β is negative and statistically significant. Only those factors with significant univariate p values (< 0.05) were selected for multivariable linear regression analysis.

* “Any fever” was not selected as a factor for multivariable linear regression, as this is a combination of 2 component factors (“multiple fevers” and “isolated fever”). Rather, these component fever factors were considered separately for multivariable linear regression.
Cognitive dysfunction is present in up to 70% of patients after aSAH,28,47 While prior studies have evaluated aSAH outcomes using the mRS, this functional test lacks the sensitivity necessary to evaluate cognitive outcomes, compared with MoCA testing. Significant clinical and radiological similarities exist between the cognitive effects of aSAH and those seen in Alzheimer’s disease, Parkinson’s disease, depression, and normal aging.2,24 The MoCA scale is effective in evaluating all of these conditions, making it an excellent test for the evaluation of cognitive outcomes after aSAH.2,30 While both the MMSE and MoCA test memory and language, the MMSE does not adequately evaluate executive function, which has been documented to be abnormal in up to 76% of aSAH patients.1 MoCA places significant emphasis on the evaluation of frontal lobe function such as attention as well as executive function, and has been studied extensively in the setting of post-stroke cognitive impairment.9,29 A recent prospective study in 80 patients with aSAH compared results obtained using both MMSE and MoCA and showed a greater area under the receiver operating characteristic curve for MoCA (0.92 vs 0.77, p = 0.009).13,5 MoCA testing can be completed in approximately 20 minutes in an alert patient with multiple cognitive domains tested, similar to those evaluated in formal, multihour, neuropsychological testing. MoCA is therefore a rapid and accurate tool for evaluating the effects of aSAH on multiple cognitive domains.

The present study has significant limitations, including its nonrandomized retrospective design and modest sample size. One potential limitation of the study includes the imbalance between the number of patients presenting with ACoA aneurysms in the treatment and control groups, with a greater proportion found in the control group. ACoA aneurysms are generally associated with more severe long-term cognitive deficits, and we did find a similar association between ACoA aneurysm location and decreased MoCA score distribution in our study. While the increased frequency of ACoA aneurysms in the control group appears to have contributed partially to this group’s poor MoCA score distribution, our multivariate analysis establishes that when controlling for this effect of ACoA aneurysm location, LDIVH treatment remained a significant positive influence on MoCA score distribution for patients with and without ruptured ACoA aneurysms. The number of patients who underwent surgical clipping included in either cohort is also potentially imbalanced with a larger proportion found within the LDIVH treatment group. Current scientific opinion considers that surgical clipping may have a greater negative effect on cognitive outcomes than endovascular treatment. If this effect is true, the imbalance found between our groups would be expected to influence poorer cognitive outcomes in the LDIVH treatment group and would decrease the chances of our study demonstrating a positive treatment effect of LDIVH on cognition, whereas we found the opposite. Additionally, in our univariate model, aneurysm treatment method was not found to be significantly associated with MoCA score distribution. Another limitation includes the time at which the MoCA was administered. Patients treated with standard therapy had a significantly longer time to MoCA testing (25.4 ± 12.6 months) compared with those treated with LDIVH (7.1 ± 7.4 months, p < 0.001). Longer duration to examination usually correlates with improvement in cognitive outcomes and thus would favor improvement in patient outcomes in the control group, which was not observed. It could be postulated that this timing difference may have masked a greater treatment effect than what was seen in our data. Improvement in physician procedural skills and progression on the learning curve also may have contributed to an improvement in outcomes.

This study is the second to demonstrate the potential safety and efficacy of the Maryland LDIVH protocol in the prevention of DND in aSAH patients. Our results provide a compelling rationale for a randomized controlled trial to evaluate LDIVH’s safety and potential efficacy in aSAH.44,45 The Aneurysmal Subarachnoid Hemorrhage Trial Randomizing Heparin (ASTROH) is a phase 2 randomized multicenter trial currently enrolling subjects to evaluate LDIVH in aSAH patients (clinical trial registration no. NCT02501434, clinicaltrials.gov).

Conclusions

Heparin is a potent antiinflammatory agent that has been correlated with a reduction in neuroinflammation associated with aSAH.46 Previous studies have demonstrated LDIVH provides protection from vasospasm and may have a positive effect on memory and cognitive outcomes.21,44 The present study suggests that the Maryland LDIVH protocol is safe and may reduce poor cognitive outcomes in patients treated after aSAH. Our results support continued enrollment efforts in ASTROH, a phase 2 randomized trial evaluating the safety and possible efficacy of LDIVH in aSAH.

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References


Disclosures
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Author Contributions
Conception and design: James, Simard. Acquisition of data: James, Shao, Carter. Analysis and interpretation of data: James, Khattar, Aljuboori, Page, Shao, Carter, Daniels, Craycroft, Gaughen, Chaudry, Rai, Everhart, Simard. Drafting the article: James, Khattar, Aljuboori, Page, Shao, Carter. Critically revising the article: James, Khattar, Aljuboori, Page, Meyer, Rai, Everhart, Simard. Reviewed submitted version of manuscript: all authors. Statistical analysis: James, Daniels, Craycroft, Rai. Study supervision: James.

Supplemental Information
Previous Presentations
Portions of this work were presented at the AHA/ASA International Stroke Conference 2015, Nashville, Tennessee, February 11, 2015; the 14th Annual Neurocritical Care Society Meeting, National Harbor, Maryland, September 15–18, 2016; the 4th SNIS International Endovascular Stroke Conference (IESC) and 2015 AANS/CNS Joint Cerebrovascular Section Annual Meeting, Nashville, Tennessee, February 9–10, 2015; and the 82nd AANS Annual Scientific Meeting, San Francisco, California, April 5–9, 2014.

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