



# HHS Public Access

Author manuscript

*J Neurosurg.* Author manuscript; available in PMC 2015 March 05.

Published in final edited form as:

*J Neurosurg.* 2013 December ; 119(6): 1611–1619. doi:10.3171/2013.8.JNS1337.

## Low-dose intravenous heparin infusion in patients with aneurysmal subarachnoid hemorrhage: a preliminary assessment

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### Abstract

**Object**—Aneurysmal subarachnoid hemorrhage (aSAH) predisposes to delayed neurological deficits, including stroke and cognitive and neuropsychological abnormalities. Heparin is a pleiotropic drug that antagonizes many of the pathophysiological mechanisms implicated in secondary brain injury after aSAH.

**Methods**—The authors performed a retrospective analysis in 86 consecutive patients with Fisher Grade 3 aSAH due to rupture of a supratentorial aneurysm who presented within 36 hours and were treated by surgical clipping within 48 hours of their ictus. Forty-three patients were managed postoperatively with a low-dose intravenous heparin infusion (Maryland low-dose intravenous heparin infusion protocol: 8 U/kg/hr progressing over 36 hours to 10 U/kg/hr) beginning 12 hours after surgery and continuing until Day 14 after the ictus. Forty-three control patients received conventional subcutaneous heparin twice daily as deep vein thrombosis prophylaxis.

**Results**—Patients in the 2 groups were balanced in terms of baseline characteristics. In the heparin group, activated partial thromboplastin times were normal to mildly elevated; no clinically significant hemorrhages or instances of heparin-induced thrombocytopenia or deep vein thrombosis were encountered. In the control group, the incidence of clinical vasospasm requiring rescue therapy (induced hypertension, selective intraarterial verapamil, and angioplasty) was 20 (47%) of 43 patients, and 9 (21%) of 43 patients experienced a delayed infarct on CT scanning. In

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### Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. Author contributions to the study and manuscript preparation include the following. Conception and design: Simard, Schreiber. Acquisition of data: all authors. Analysis and interpretation of data: Simard, Aldrich, Polifka, Beaty. Drafting the article: Simard, Schreiber, James, Polifka, Beaty. 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: Simard. Statistical analysis: Simard.

the heparin group, the incidence of clinical vasospasm requiring rescue therapy was 9% (4 of 43,  $p = 0.0002$ ), and no patient suffered a delayed infarct ( $p = 0.003$ ).

**Conclusions**—In patients with Fisher Grade 3 aSAH whose aneurysm is secured, postprocedure use of a low-dose intravenous heparin infusion may be safe and beneficial.

### Keywords

subarachnoid hemorrhage; cerebral vasospasm; inflammation; heparin; vascular disorders

Aneurysmal subarachnoid hemorrhage (aSAH) is associated with numerous adverse sequelae.<sup>4,63</sup> Patients who survive the initial hemorrhage are at high risk for secondary brain injury induced by vasospasm, microthrombi, oxidative damage, and inflammation, resulting in cerebral infarction, neuronal cell death, and white matter loss, and culminating in delayed focal neurological deficits and long-term cognitive and psychosocial deficits.<sup>11,24,42,48,53,54,58,62,70,77</sup> Collectively, the neurological, cognitive, and neuropsychological abnormalities are referred to as aSAH-induced delayed neurological deficits (DNDs). To date, effective prophylactic therapy for aSAH-induced DNDs has been elusive.<sup>14,52</sup>

Heparin is a member of a family of polyanionic polysaccharides called glycosaminoglycans, composed of hexuronic acid and D-glucosamine residues joined by glycosidic linkages.<sup>6</sup> Unfractionated heparin is a heterogeneous mixture of polysaccharide chains of varying lengths, ranging from 3 to 30 kD.<sup>37</sup> Heparin (always used here to refer to unfractionated heparin) has the highest negative charge density of any known biological molecule and, as a result, has a high propensity to bind to positively charged molecules and surfaces. More than 100 heparin-binding proteins have been identified,<sup>76</sup> with the growing list including numerous plasma proteins, proteins released from platelets, cytokines, chemokines, and other small biologically active molecules, as well as endothelial cells themselves.<sup>10,23,27,51</sup> Although clinically used almost exclusively for its anticoagulant properties, heparin binding can interrupt numerous other biological pathways.<sup>47</sup>

Heparin is a pleiotropic drug that antagonizes many of the molecular mechanisms that have been implicated in secondary brain injury after aSAH.<sup>60</sup> Among its wide-ranging effects, heparin complexes with free hemoglobin itself, including oxyhemoglobin;<sup>1</sup> it blocks the activity of free radicals, including reactive oxygen species;<sup>18</sup> it antagonizes endothelin-mediated vasoconstriction;<sup>7,44,75</sup> and it binds to several growth factors, thereby imparting antimitogenic<sup>25,26,36</sup> and antifibrotic<sup>57</sup> effects. Arguably, one of its most important effects is to act as a potent, nonconventional antiinflammatory agent.<sup>17,29,66,67,76</sup> The antiinflammatory effect of heparin is unrelated to anticoagulant activity.<sup>45,55</sup> Heparin binds to several cytokines and all chemokines; it inhibits the production and release of proinflammatory factors, including interleukin (IL)-1 $\beta$ , IL-6, and tumor necrosis factor- $\alpha$ .<sup>2,28,46</sup> It inhibits the activation of nuclear factor  $\kappa$ B;<sup>76</sup> it inhibits RAGE (receptor for advanced glycation end products)-mediated inflammation;<sup>55</sup> and it attenuates endothelial dysfunction by enhancing nitric oxide and prostacyclin release.<sup>50</sup> Recent work has shown that low-dose intravenous heparin infusion significantly reduces neuroinflammation (neutrophils, activated phagocytic microglia, nuclear factor  $\kappa$ B, tumor necrosis factor- $\alpha$ ,

and IL-1 $\beta$ ) as well as transsynaptic apoptosis in a preclinical model of aSAH involving eloquent cortex.<sup>61</sup> To our knowledge, no other compound has been identified that exhibits such a broad diversity of biological effects that are so intimately relevant to mechanisms implicated in aSAH-induced DNDs. The very multiplicity of mechanisms targeted by heparin suggests that it may be useful as a multitargeted prophylactic agent to ameliorate the wide-ranging abnormalities induced by aSAH.

For several years at our institution, some patients with high-grade aSAH who were treated surgically for a supratentorial saccular aneurysm have been managed postoperatively using a low-dose intravenous heparin infusion. Here, we report on a retrospective analysis of the outcome of these patients, comparing them with patients with similar baseline characteristics who were managed concurrently, but with conventional subcutaneous heparin twice daily as prophylaxis against deep vein thrombosis (DVT). Briefly, our experience suggests that a low, nonanticoagulating dose of heparin administered by constant intravenous infusion may be safe and beneficial in these patients.

## Methods

The Institutional Review Board of the University of Maryland approved the protocol for a retrospective review. Patient records during the period between January 2006 and May 2011 were searched for the ICD-9-CM diagnosis code 473.3, which identified 411 patients who had undergone craniotomy for clipping of a supratentorial aneurysm. Computed tomography angiography (CTA) or catheter digital subtraction angiography (DSA) was used to confirm the presence of an aneurysm. In cases of aSAH, the severity of the hemorrhage was graded using the classification of Fisher et al.<sup>22</sup> Of the 411 cases identified, 144 were excluded because they were Grade 0 (unruptured) supratentorial aneurysms, 177 were excluded because they were ruptured supratentorial aneurysms with Fisher Grade 1, 2, or 4 hemorrhages, or ruptured supratentorial aneurysms with Fisher Grade 3 hemorrhages that presented more than 36 hours after their ictus. These exclusions left 90 consecutive patients with ruptured supratentorial aneurysms presenting with Fisher Grade 3 hemorrhages within 36 hours of their ictus who underwent surgery. Of the 90 patients who met the initial screening criteria, 4 were excluded because they had either a giant or a fusiform aneurysm, or because they had a significant hemiparesis due to a preoperative intracerebral hematoma. The remaining 86 patients are the subject of this report.

The 86 patients all underwent craniotomy for aneurysm clipping within 48 hours of their ictus. All patients were treated by one of 2 faculty neurosurgeons, one of whose practice included the postoperative administration of a low-dose intravenous heparin infusion (heparin group), and the other whose practice did not (control group). All other aspects of patient management were identical for both surgeons. Patients in both groups were treated concurrently; there were no differences in variables such as treatment eras, ICU policy or ICU attending physicians, residents, or nurse practitioners. No patient was excluded because of a confirmed surgical injury or an untoward intraoperative event. There was no bias in assigning patients to one or the other surgeon; assignments were based simply on a predetermined call schedule. Both surgeons used temporary clipping for similar indications.

Of the 86 patients who met the inclusion criteria, 43 patients were treated with a low-dose intravenous heparin infusion, and 43 were not.

### **The Maryland Low-Dose Intravenous Heparin Infusion Protocol**

The protocol for the low-dose intravenous heparin infusion was as follows: 1) after surgery, CT scanning and CTA were performed to document the absence of any postoperative complication and to confirm aneurysm obliteration; 2) an intravenous infusion of unfractionated heparin, 8 U/kg/hr (no loading dose), was begun 12 hours after craniotomy; and 3) 12 hours later, the infusion was increased to 9 U/kg/hr intravenously, and after an additional 12 hours, the infusion was increased to 10 U/kg/hr intravenously. The infusion generally was maintained for 14 days (12–16 days) after the ictus.

Values of activated partial thromboplastin time (aPTT) were monitored twice daily for 5 days. The gradual increase in the rate of infusion typically yielded values of aPTT that were normal to mildly elevated (see *Results*). If values exceeded 45 seconds within the first 3 days after surgery (but not later), the infusion rate was decreased by one step for 12 hours before resuming the higher level.

### **Standard Management of Patients With aSAH**

All patients were treated in accordance with the *Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage*, including initial maintenance of euvoemia, administration of nimodipine, and, when appropriate, drainage of CSF.<sup>4</sup> For patients in the control group, prophylaxis against DVT included subcutaneous injections of unfractionated heparin (5000 U) twice daily. Patients treated with the low-dose intravenous heparin infusion did not receive subcutaneous heparin injections.

Radiological examinations, including CT, CTA, or DSA, as appropriate, were obtained routinely during the first 24 hours after surgery and periodically thereafter to check for hydrocephalus or clearance of intracranial blood, or at the discretion of the treating physician, or whenever there was neurological deterioration of any sort, focal or nonfocal. In the heparin group, CTA also was performed at the end of the infusion.

In the case of focal or nonfocal neurological deterioration suggestive of symptomatic vasospasm, even before radiographic confirmation of angiographic vasospasm, patients were given hypervolemic therapy consisting of a fluid bolus and an increase in the infusion rate of intravenous fluid.<sup>4</sup> In addition, patients with symptomatic vasospasm were treated with induced hypertension using a phenylephrine infusion to increase systolic blood pressure by 20%, up to a maximum dose of 200 µg/min.<sup>49</sup> When persistent clinical deterioration was accompanied by angiographic vasospasm that was not immediately responsive to induced hypertension, patients were treated with selective intraarterial verapamil or angioplasty.<sup>33,41</sup> In some cases when imaging showed moderate to severe angiographic vasospasm, even in neurologically intact patients, hypervolemic therapy or induced hypertension was implemented.

## Data Compilation

Patient medical records, including computerized hospital records and clinic notes, were reviewed by 2 neurosurgeons (N.B. and A.P.) for demographic, clinical, radiographic, and outcome data.

The severity of aSAH was scored based on the first available CT scan, obtained either before or after admission to the University of Maryland hospital. All CT scans were reviewed by 2 neurosurgeons (N.B. and A.P.) who together assigned a Fisher Grade.<sup>22</sup> In accordance with the original description,<sup>22</sup> CT scans with a pattern of aSAH fitting the criteria for Fisher Grade 3 aSAH but also showing moderate to large amounts of intraventricular or intracerebral hemorrhage were scored as Fisher Grade 3.

The occurrence of angiographic vasospasm, scored as a binary variable, was determined from a review of all CTA and DSA studies by 2 neurosurgeons (A.P. and N.B.) and independently by experienced neuroradiologists from the University of Maryland. When compared with baseline studies, any study showing evidence of angiographic vasospasm in any vascular territory, regardless of severity or of the clinical/neurological status of the patient, was scored as having angiographic vasospasm. The severity of angiographic vasospasm was not recorded.

The occurrence of clinical vasospasm, scored as a binary variable, was determined from a review of the neurological status of the patients and was scored when focal neurological deterioration was accompanied by angiographic vasospasm in the appropriate vascular territory, or when nonfocal neurological deterioration was accompanied by diffuse or multiterritory angiographic vasospasm.

The occurrence of new ischemia-related CT hypodensities was determined from a review of all CT scans by 2 neurosurgeons (N.B. and A.P.) and independently by experienced neuroradiologists from the University of Maryland. Findings on CT scans obtained during hospitalization and after discharge were correlated with CTA or DSA and neurological examination, to ascertain whether new hypodensities were attributable to vasospasm (within a discrete vascular or watershed territory), as opposed to being due to an intraparenchymal hemorrhage, intraventricular catheter placement, surgical retraction, or surgery-related loss of a perforating artery.<sup>30</sup>

## Statistical Analysis

Calculations were performed using InStat (version 3.1, GraphPad Software, Inc.). Parametric data are reported as the mean  $\pm$  SD. Parametric and nonparametric data were analyzed using Student's unpaired t-test and the Mann-Whitney U-test, respectively. Rates were analyzed using a 2-way contingency table and Fisher's exact test (2-tailed). p values < 0.05 were considered significant.

## Results

### Baseline Characteristics

Eighty-six patients with Fisher Grade 3 aSAH due to rupture of a supratentorial saccular aneurysm were included in this study, with 43 patients each in the control and the heparin groups. Their baseline characteristics are shown in Table 1. There were no statistically significant differences between groups in terms of age, sex, presenting neurological status (World Federation of Neurosurgical Societies [WFNS] grade and Glasgow Coma Scale [GCS] score), hypertension, use of statins,<sup>65</sup> or use of tobacco or cocaine.<sup>9,72</sup> Aneurysms in the control versus heparin groups were located at the posterior communicating artery (6 vs 14), anterior choroidal artery (1 vs 2), internal carotid artery bifurcation (2 vs 2), anterior communicating artery (26 vs 13), middle cerebral artery (MCA) bifurcation (6 vs 10), and pericallosal artery (2 vs 2).

### Safety

The low-dose intravenous heparin infusion was started 12 hours after surgery. The average length of time between the start of heparin infusion and the ictus was  $40.7 \pm 7.9$  hours. The protocol for the low-dose intravenous heparin infusion, which began with 8 U/kg/hr and progressed over 36 hours to 10 U/kg/hr intravenously, resulted in values of aPTT that were generally in the range of normal to mildly elevated (Fig. 1).

None of the 43 patients in the heparin group incurred a bleeding complication, DVT, or heparin-induced thrombocytopenia (HIT).<sup>12</sup> One patient from the heparin group had a thin postoperative subdural hematoma that was diagnosed immediately after surgery on a postoperative CT scan. The heparin protocol was started at 12 hours despite this collection. Subsequent CT scans never showed expansion of this collection.

### Vasospasm

The incidence of angiographic vasospasm in the control and heparin groups was 26 (60%) of 43 patients and 25 (58%) of 43 patients, respectively ( $p = 1$ ) (Fig. 2). In the control group, rescue therapy (induced hypertension or selective intraarterial verapamil with or without angioplasty; Table 2) was implemented in 21 (49%) of 43 patients, whereas in the heparin group, rescue therapy was implemented in 4 (9.3%) of 43 patients ( $p < 0.0001$ ). In the control group, the reason for performing CTA that prompted initiation of rescue therapy was new focal neurological deficit (12 patients), new nonfocal neurological deterioration (8 patients), and discretionary investigation with no neurological deterioration (1 patient), for an overall incidence of symptomatic vasospasm of 47% (20 of 43 patients) (Fig. 2). In the heparin group, the reason for performing CTA that prompted initiation of rescue therapy was new focal neurological deficit (3 patients) and new nonfocal neurological deterioration (1 patient), for an overall incidence of symptomatic vasospasm of 9% (4 of 43 patients;  $p = 0.0002$ ) (Fig. 2).

### Computed Tomography Infarcts

Nine (21%) of 43 patients in the control group had vasospasm-related infarcts (Figs. 2 and 3A and B). The vascular territories involved were the left MCA (4 patients), right MCA (2



patients), anterior cerebral artery (2 patients), and bilateral anterior cerebral artery and right MCA territories (1 patient). In all cases that were scored as infarcts, accompanying neurological deficits confirmed the significance of the CT findings. There were no vasospasm-related infarcts in the heparin group ( $p = 0.003$ ) (Figs. 2 and 3C and D).

### Clinical Outcomes

Recommendations for discharge to home versus a rehabilitation center were made independently by physical therapists at the time of discharge. In the control group, 17 patients were discharged home and 25 were discharged to rehabilitation centers, whereas in the heparin group, 27 patients were discharged home and 16 were discharged to rehabilitation centers ( $p = 0.05$ ).

In the control group 1 patient, who had not experienced clinical vasospasm, died of cardiopulmonary complications during an extended hospital stay. Of the 9 patients with vasospasm-related infarcts, 1 was discharged home with a mild residual aphasia, and 8 were transferred to rehabilitation centers with neurological deficits including hemiparesis, dense hemiplegia, dense aphasia, and bilateral lower-extremity weakness. At 6 weeks, 3 of these patients remained in rehabilitation; 2 of them had experienced vasospasm-related left MCA infarcts, and the third had developed chronic pulmonary failure worsened by a preexisting severe chronic obstructive pulmonary disease. The remaining 33 patients were seen at 6-week follow-up and were judged to have good to excellent neurological outcomes.

In the heparin group, no patient died in-hospital, and no patient had a persistent focal neurological deficit. Follow-up data were not available for 6 patients; 3 of these patients were discharged home directly from the hospital, and 3 were transferred to rehabilitation facilities, from which they had been discharged already by the time of their scheduled 6-week follow-up. No patient from the heparin group remained in rehabilitation at 6 weeks. Of the 37 patients who returned for 6-week follow-up, all self-reported good to excellent recovery with near-baseline or baseline memory and cognition.

### Discussion

This is the first report to examine the use of a low-dose intravenous heparin infusion as prophylaxis against DNDs in the management of patients with aSAH. The use of an anticoagulating dose of heparin (2500–3500 U subcutaneously every 6 hours,<sup>39,40</sup> or constant intravenous infusion<sup>71</sup>) has been advocated previously to reduce complications of aSAH and was reported to reduce ischemic events in patients with aSAH undergoing carotid ligation for aneurysm treatment.<sup>8,39,40,71</sup> Anticoagulation with low-molecular-weight heparin (enoxaparin) was found to be promising in one study,<sup>74</sup> but this finding was not replicated by a second group of investigators.<sup>35,59</sup> Regardless, the use of heparin has not gained support among neurosurgeons, presumably because of the notion that an anticoagulating dose would be required, along with the concern that an anticoagulating dose might predispose to hemorrhagic complications.<sup>73</sup> However, under physiological conditions, heparin does not have fibrinolytic activity,<sup>64</sup> suggesting that the risk of bleeding may not be increased once a stable fibrin clot has formed. Our experience indicates that low-dose

heparin administered by constant intravenous infusion may be safe and beneficial, independent of anticoagulation.

### Safety

The specific protocol used for the low-dose intravenous heparin infusion, which began with 8 U/kg/hr and progressed over 36 hours to 10 U/kg/hr intravenously, combined with the delay of 12 hours after surgery before starting the infusion, yielded a favorable safety profile with no untoward side effects. Only modest elevations in aPTT were observed, and no hemorrhagic complications were identified.<sup>8,71</sup> Furthermore, no case of HIT or DVT was identified. However, the absence of HIT, DVT, and hemorrhagic complications in the present series must be viewed with caution. The risk of HIT generally is low, with an incidence of approximately 3% associated with infusion of an anticoagulating dose,<sup>12</sup> and of 1.4%–5.2% associated the dose used for DVT prophylaxis.<sup>34</sup> The incidence of DVT in aSAH is 18%.<sup>56</sup> Larger studies will be needed to establish the true safety of the low-dose intravenous heparin infusion protocol described here. Alternatively, nonanticoagulating N-desulfated heparin, which retains other biological properties and effects of heparin, including antiinflammatory effects,<sup>3,55</sup> should be considered for use in future studies of aSAH, given its better safety profile regarding anticoagulation.

### Efficacy

The incidence of angiographic vasospasm of any degree was not affected by the low-dose intravenous heparin infusion, consistent with the 2 groups being well balanced in terms of risk factors. Although we did not assess the severity of angiographic vasospasm in the 2 groups, significantly fewer patients in the heparin group developed symptomatic vasospasm and related infarcts on CT scanning.

Cerebral infarction and functional outcome are regarded as the preferred outcome measures to investigate the true impact of an intervention after aSAH.<sup>19</sup> Cerebral infarction is strongly associated with poor outcome after aSAH,<sup>69</sup> and symptomatic vasospasm is the most important factor predisposing to infarction.<sup>21</sup> In the present study, the incidence of vasospasm-related infarcts in the control group was 21%, which is comparable to previous reports in patients with Fisher Grade 3 aSAH.<sup>30</sup> By contrast, no patient in the heparin group developed a vasospasm-related infarct or lasting focal neurological deficit. Most of the patients with vasospasm-related infarcts in the control group (8 of 9) had poor functional outcomes, and most of these patients (7 of 8) were conscious and either neurologically normal or only confused upon presentation.

Patients who received the intravenous heparin infusion and who returned for evaluation at 6 weeks had overall favorable clinical outcomes, as judged by neurological examinations and by self-reported cognitive and memory functions. Further standardized testing will be required to confirm this tentative finding regarding cognition, but if true, such an effect of heparin could have a large impact on quality of life.

Starting a low-dose heparin infusion in patients several days after a substantial sentinel hemorrhage or after clinical vasospasm has developed may not be as beneficial (J. M. Simard, unpublished observation), reinforcing that this protocol needs to be started soon



after the ictus. The protocol described here, including the maximum dose of 10 U/kg/hr, was developed before the US Food and Drug Administration changed its reference standard for heparin,<sup>68</sup> which resulted in a 10% lowering of its apparent potency. Future studies of heparin in aSAH will need to take this into account, as well as the possibility that higher doses of heparin may have greater efficacy.

### Route and Manner of Administration

The dose and timing of heparin administration required for a beneficial effect in aSAH appear to differ from that required to alter coagulation. For a 70-kg patient, infusion of 10 U/kg/hr of heparin results in a total daily dose of 16,800 U, which yielded aPTT values that were normal to mildly elevated. By comparison, a total daily dose of 10,000 U (5000 U twice daily) was used in the control patients for DVT prophylaxis. It is possible that the higher daily dose received by the intravenous heparin group accounts for the better outcomes, compared with controls. However, the pharmacokinetics of heparin administered subcutaneously twice daily can be highly variable, due in part to a dose-dependent serum half-life that plateaus within 30 minutes.<sup>5,13,43</sup> Evidence from other studies indicates that the route (intravenous vs subcutaneous) and the manner (continuous infusion vs twice daily injection) of administration of heparin can play significant roles in obtaining a favorable therapeutic effect unrelated to anticoagulation.<sup>16</sup>

The route and manner of administration also may account for the conflicting effects reported in trials with enoxaparin (1 subcutaneous injection daily) after aSAH.<sup>35,59,74</sup> Notably, low-molecular-weight heparin exhibits an antiinflammatory profile similar to that of unfractionated heparin<sup>28,29</sup> and may have a better safety profile regarding bleeding.<sup>15,31</sup> However, continuous intravenous infusion of low-molecular-weight heparin<sup>20,38</sup> has not been examined in patients with aSAH.

### Study Limitations

This is a preliminary study of the potential safety and efficacy of low-dose intravenous heparin infusion in patients with high-grade aSAH undergoing craniotomy for clipping of a supratentorial aneurysm. This study has several limitations, including its open label, nonrandomized, retrospective design, all of which can introduce bias, as well as its modest sample size. We scored angiographic spasm as a binary variable (none vs any degree), precluding an assessment of whether heparin decreases the severity of angiographic vasospasm. However, the direct comparison of outcomes with those of patients having similar baseline characteristics who were treated concurrently at the same institution gives weight to our conclusion. Computed tomography scans may be unreliable when used by themselves to identify vasospasm-related infarcts,<sup>32</sup> but all cases here that were scored as infarcts were corroborated by appropriate accompanying neurological deficits. Evaluating neurocognitive function based on self-reported information is not as robust as formal neuropsychological evaluation, but in practice, patients and their immediate family members are seldom reluctant to complain about life-altering neurocognitive abnormalities.

## Conclusions

The Maryland low-dose intravenous heparin infusion protocol appeared to be safe and may be an efficacious prophylaxis against DNDs associated with severe aSAH. Patients administered a low-dose intravenous heparin infusion within 48 hours of their ictus experienced significantly fewer occurrences of symptomatic vasospasm and infarcts compared with controls. The favorable results reported in this study, bolstered by strong physiological<sup>60</sup> and preclinical data,<sup>61</sup> suggest that a multicenter dose and safety assessment of intravenous heparin infusion (conventional unfractionated heparin, low-molecular-weight heparin, or nonanticoagulating N-desulfated heparin),<sup>3,55</sup> may be warranted.

## Addendum

Because the US Food and Drug Administration changed its reference standard for heparin, we recently changed the Maryland low-dose intravenous heparin infusion protocol to 8 U/kg/hr progressing over 36 hours to 12 U/kg/hr.

## Abbreviations used in this paper

<b>aPTT</b>	activated partial thromboplastin time
<b>aSAH</b>	aneurysmal subarachnoid hemorrhage
<b>CTA</b>	CT angiography
<b>DND</b>	delayed neurological deficit
<b>DSA</b>	digital subtraction angiography
<b>DVT</b>	deep vein thrombosis
<b>GCS</b>	Glasgow Coma Scale
<b>HIT</b>	heparin-induced thrombocytopenia
<b>MCA</b>	middle cerebral artery
<b>WFNS</b>	World Federation of Neurosurgical Societies

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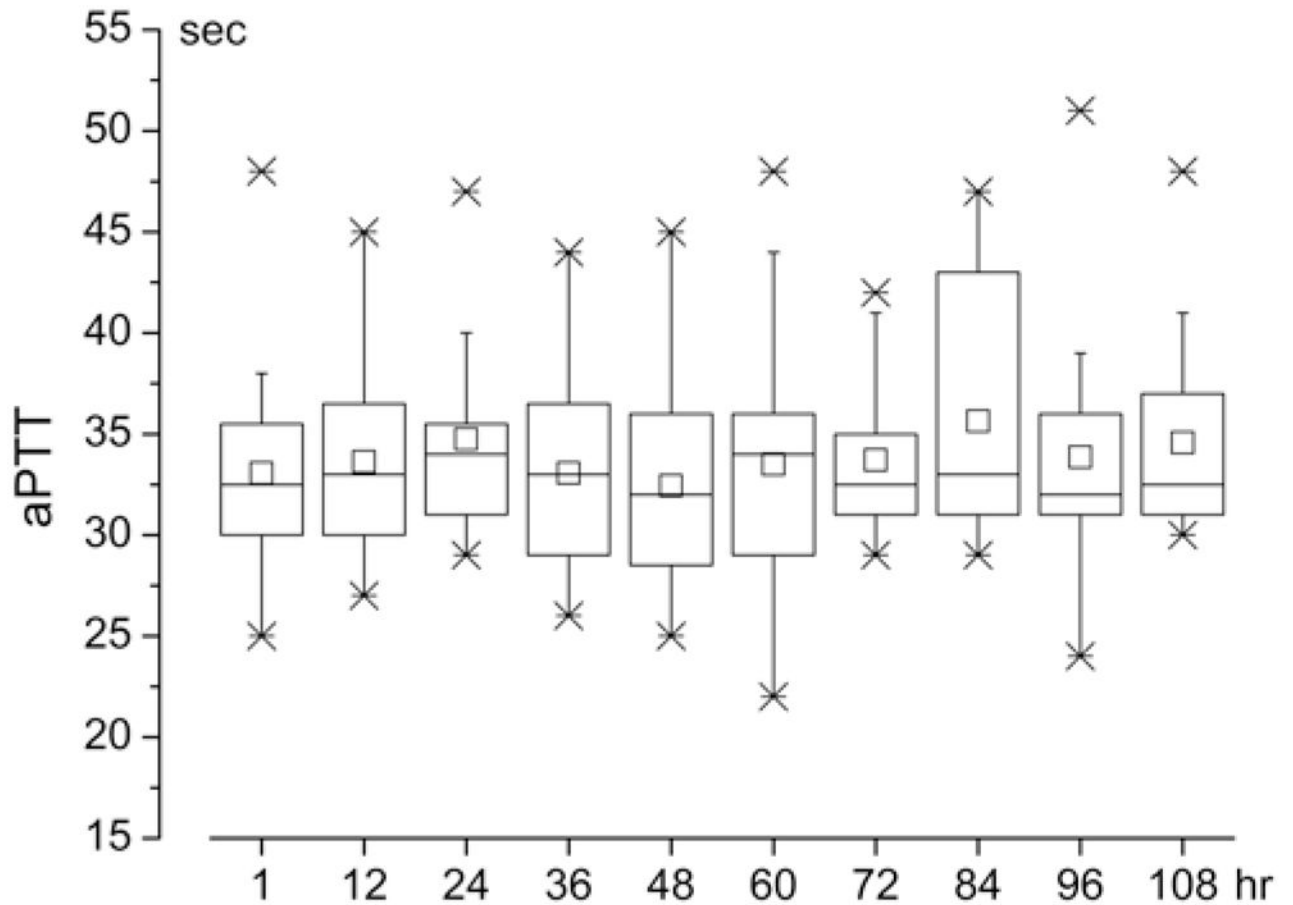
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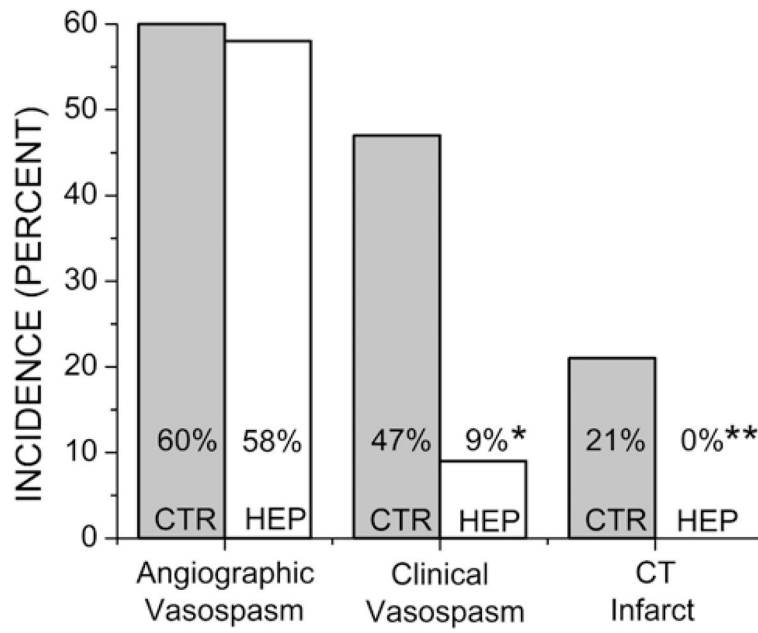
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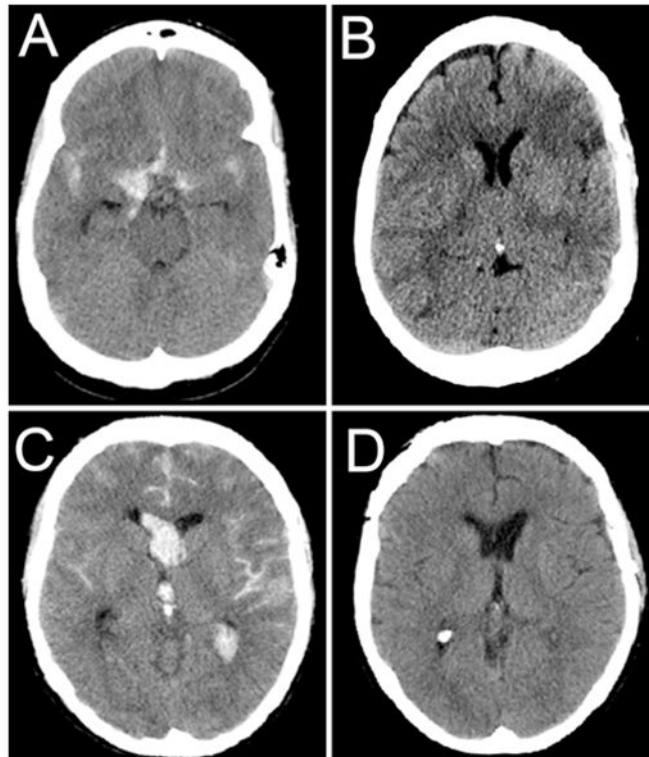




**Fig. 1.** Values of aPTT associated with the Maryland low-dose intravenous heparin infusion protocol. Box plots as a function of time, of values of aPTT in patients administered the Maryland low-dose intravenous heparin infusion protocol (8 U/kg/hr by constant intravenous infusion for 12 hours, increasing by 1 U/kg/hr at 12-hour intervals to a final maintenance dose of 10 U/kg/hr intravenous). In the box plots, the *large boxes* indicate the 25th and 75th percentiles; *whiskers*, the 5th and 95th percentiles; *x*, the 1st and 99th percentiles; *–*, the maximum and minimum; *horizontal line within the box*, the median; and the *small square*, the mean. Normal aPTT at the University of Maryland, 25–38 seconds.



**Fig. 2.** Vasospasm-related outcomes. The incidence of angiographic vasospasm, clinical vasospasm, and CT infarctions in the control (CTR) and heparin (HEP) groups, as indicated. \*p = 0.0002; \*\*p = 0.003.



**Fig. 3.**

Computed tomography scans obtained in representative patients from the control and heparin groups. **A and B:** Admission (A) and follow-up (B) CT scans obtained in a 50-year-old patient who presented with a ruptured anterior communicating artery aneurysm. The patient was neurologically intact upon presentation. The patient underwent successful surgical clipping. The patient's hospital course was complicated by clinical vasospasm with associated aphasia. Despite multiple intravascular interventions, the patient developed frontal and parietal infarcts. At follow-up, the patient's aphasia was improving. **C and D:** Admission (C) and follow-up (D) CT scans obtained in a 47-year-old patient who presented with a ruptured anterior communicating artery aneurysm. The patient was comatose upon presentation with a GCS score of 6T. The patient underwent successful surgical clipping and was subsequently treated with a low-dose intravenous heparin infusion. The patient developed angiographic vasospasm but did not require rescue intervention. At follow-up, the patient was neurologically normal, including normal cognition and short-term memory.

**TABLE 1**

## Patient baseline characteristics

Parameter	Control Group (n = 43)*	Heparin Group (n = 43)*	p Value
mean age (yrs)	55.3 ± 12.9	54.5 ± 11.3	0.98 <sup>†</sup>
female sex	34	32	0.80
WFNS grade			
mean	2.0 ± 1.3	2.5 ± 1.6	0.16 <sup>†</sup>
median	2.0	2.0	0.23 <sup>†</sup>
3	10	16	0.24
GCS score			
mean	13.1 ± 2.9	12.2 ± 3.6	0.23 <sup>†</sup>
median	14	14	0.33 <sup>†</sup>
7	6	7	1.0
hypertension	21	20	1.0
statin use	8	6	0.77
tobacco use	22	25	0.67
cocaine use	3	1	0.62

\* Values represent the number of patients unless otherwise noted. Mean values are presented as the mean ± SD.

<sup>†</sup> Student's t-test or Mann-Whitney U-test; otherwise, from Fisher's exact test (2-tailed).

**TABLE 2**

## Use of rescue therapy for vasospasm

Rescue Therapy	Control Group (n = 43)	Heparin Group (n = 43)	p Value <sup>†</sup>
phenylephrine infusion *	14	4	0.016
microcatheter-directed therapy <sup>‡</sup>	12	3	0.021

\* Patients treated with a phenylephrine infusion had their blood pressure titrated to a systolic blood pressure that resulted in resolution of their symptoms or to a maximum of 200 mg/minute.

<sup>†</sup> Fisher's exact test (2-tailed).

<sup>‡</sup> Microcatheter-directed therapy involved selective angioplasty or intraarterial infusion of verapamil to a total dose no greater than 20 mg in a 24-hour period.