A c u t e  S D H  carries  a  high  risk  of  death. 1 2 3  The  op-  
imal treatment for acute SDH remains uncertain,  
but usually includes reversal of coagulopathy,  
early surgical evacuation of the hematoma, and medical  
supportive care including management of elevated in-  
tracranial pressure, ventilator support, and treatment of  
ICU comorbidities. Previously reported factors that are  
associated with a poor prognosis in patients with acute  
SDH include advanced age, baseline low GCS score,  
hypotension, hypoxia, pupillary abnormalities, time un-  
til surgery, elevated intraoperative intracranial pressure,  
and CT findings of large hematoma volume, large degree  
of midline shift, compression of basal cisterns, or associ-  
ated subarachnoid hemorrhage. 1 2 However, many of  
these factors are not modifiable. It has been reported  
that coagulopathy in patients with ICH is associated with  

Coagulopathy and inhospital deaths in patients with acute  
subdural hematoma  
Clinical article  

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O b ject. Acute subdural hematoma (SDH) is one of the most lethal forms of intracranial injury; several risk  
factors predictive of a worse outcome have been identified. Emerging research suggests that patients with coagulopathy  
and intracerebral hemorrhage have a worse outcome than patients without coagulopathy but with intracerebral hem-  
orrhage. The authors sought to determine if such a relationship exists for patients with acute SDH.  

M e thods. The authors conducted a retrospective analysis of consecutive patients admitted to a neurosciences in-  
tensive care unit with acute SDH over a 4-year period (January 1997–December 2001). Demographic data, laboratory  
values, admission source, prior functional status, medical comorbidities, treatments received, and discharge disposi-  
tion were recorded, as were scores on the Acute Physiology, Age, and Chronic Health Evaluation III (APACHE III).  
Coagulopathy was defined as an internal normalized ratio > 1.2 or a prothrombin time ≥ 12.7 seconds. Univariate  
and multivariate analyses were performed on 244 patients to determine factors associated with worse short-term  
outcomes.  

R esults. The authors identified 248 patients with acute SDH admitted to the neurointensive care unit during the  
study period, of which 244 had complete data. Most were male (61%), and the mean age of the study population was  
71.3 ± 15 years (range 20–95 years). Fifty-three patients (22%) had coagulopathy. The median APACHE III score  
was 43 (range 11–119). Twenty-nine patients (12%) died in the hospital. Independent predictors of in-hospital death  
included APACHE III score (odds ratio [OR] 4.4, 95% confidence interval [CI] 1.4–13.4, p = 0.011) and coagulopa-  
thy (OR 2.7, 95% CI 1.1–7.1, p = 0.037). Surgical evacuation of acute SDH was associated with reduced inhospital  
deaths (OR 0.2, 95% CI 0.1–0.6, p = 0.003).  

C onclusions. Coagulopathy is independently associated with inhospital death in patients with acute SDH. Time  
to treatment to correct coagulopathy using fresh frozen plasma and/or vitamin K was prolonged.  

( D O I : 1 0 . 3 1 7 1 / J N S / 2 0 0 8 / 1 0 9 / 1 0 / 0 6 6 4 )  

K ey w o r d s  •  a c u t e  s u b d u r a l  h e m a t o m a  •  c o a g u l o p a t h y  •  
inhospital death • outcome  

A b b r e v i a t i o n s  u s e d  i n  t h i s  p a p e r :  A P A C H E  III = Acute Phys-  
ology, Age, and Chronic Health Evaluation III; CI = confidence inter-  
vall; FFP = fresh frozen plasma; GCS = Glasgow Coma Scale; ICH =  
intracerebral hemorrhage; ICU = intensive care unit; INR = interna-  
tional normalized ratio; LOS = length of stay; NICU = neurosciences  
ICU; OAT = oral anticoagulation therapy; OR = odds ratio; PCC =  
prothrombin complex concentrate; PT = prothrombin time; rFVIIa =  
recombinant activated factor VIIa; SD = standard deviation; SDH =  
subdural hematoma.
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a poor outcome;\textsuperscript{5,7,15} whether this relationship is similar in patients with acute SDH remains uncertain. Thus, we chose to determine if coagulopathy is independently associated with poor outcome in patients with acute SDH, given that this factor may be reversible and could potentially lead to improved patient outcomes with rapid treatment.

**Methods**

**Patient Population and Data Collection**

We received approval to perform this study from our hospital institutional review board. The 10-bed NICU at University Hospitals Case Medical Center exclusively admits critically ill patients with neurological and neurosurgical problems. We reviewed the hospital’s prospective database of all ICU admissions and identified 248 patients admitted to the NICU with acute SDH between January 1997 and December 2001. We included only 244 patients in our analysis due to incomplete data in 4 patients.

We extracted the following information from the database: demographic data, admission APACHE III score, admission coagulation status (PT, INR and partial thromboplastin time), admission source, patient characteristics, prior functional status, GCS score on admission, medical comorbidities, medical and surgical treatment received, hospital and NICU LOS, mechanical ventilation status, withdrawal of care status, cause of death, and discharges disposition. Coagulation status was defined as an INR $\geq 1.2$ or PT $\geq 12.7$ seconds, which is $> 2$ SDs above the mean used at our institution and was also the consensus level used by the neurosurgeons and neurointensivists at this institution to initiate corrective measures in patients with ICHs. The APACHE III score is a general purpose severity-of-illness scoring system that was collected at our institution. The maximum APACHE III score is 299, and a higher score is associated with increased mortality rates. The value of APACHE III scoring is in the stratification of risk and measurement of disease severity.\textsuperscript{20}

Demographic data included age, sex, and race. Admission source was categorized into 1 of the following: direct admission, emergency room, hospital unit bed or other hospital unit transfer, operating room, other ICU, or recovery room. Patient characteristics included medical conditions, anticoagulant use, and smoking status. We used the modified Rankin Scale to determine functional status before admission.\textsuperscript{22} Our definitions of disability included the following: 1) independent, able to carry out all activities without any help; 2) mild disability, unable to carry out all activities but able to look after own affairs without assistance; 3) moderate disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; and 4) severe disability, bedridden, incontinent, and requiring constant nursing care and assistance. Two of the investigators (J.I.S. and E.S.F.) obtained the disability information available in the medical records. We determined interobserver agreement for the assessment of disability in 50 randomly selected patients. The 2 investigators agreed on the degree of handicap in 34 patients; they differed by 1 grade of handicap in 14 patients and by 2 grades of handicap in 2 patients (weighted kappa $= 0.6$). Medical treatment data included time until reversal of coagulopathy and type of treatment used to correct coagulopathy. We collected basic information regarding the presence or absence of treatment with FFP and/or vitamin K; however, we do not have the data regarding the number of units of FFP, time until treatment with FFP, vitamin K dose, and route of administration. Surgical treatment included bur hole drainage or craniotomy with SDH evacuation. The ICU discharge disposition was categorized according to the following: hospital unit, other ICU, step-down unit (transitional unit), other hospital, home, or dead. Hospital discharge disposition included home, skilled nursing facility, other nursing or rehabilitation center, or dead. We determined whether or not patients were deceased at 6 months by reviewing the Social Security Death Index. We did not have initial head CT scan data available in most patients and thus we did not include it in our study.

**Statistical Analysis**

We used the chi-square test, t-test, and Mann–Whitney U-test as appropriate to determine statistically significant differences between the patients with or without coagulopathy. We defined statistical significance as a probability value $\leq 0.05$. We used logistic regression analysis to identify covariates that were independently associated with death. We included in the model those covariates that were found to be significant in the univariate analysis. We also investigated collinearity and interaction between the covariates and found none. Data were analyzed using JMP (SAS institute) and NCSS 2000 statistical software.

**Results**

We analyzed 244 consecutive patients with acute SDH. The mean age of the study population ($\pm$ SD) was 71.3 $\pm$ 15 years (range 20–95 years), 148 (61%) were male, and 53 (22%) were coagulopathic (defined as INR $> 1.2$ or PT $\geq 12.7$ seconds; Table 1). Of the coagulopathic patients, 31 (58%) had been taking the oral anticoagulant warfarin. The mean INR in coagulopathic patients was 2.67 $\pm$ 2.81. Most patients (64%) were admitted from the operating or recovery room following surgery for acute SDH evacuation, and most (88%) had mild or no disability prior to hospital admission. The median APACHE III score was 43 (range 11–119) and the proportion of patients with a GCS score $< 8$ was 17%. Coagulopathic patients had a significantly higher baseline APACHE III score and a higher proportion of coma (GCS score $< 8$) compared with noncoagulopathic patients (Table 2). The cause of coagulopathy was not elucidated in all patients. However, from the data collected, the majority of patients had been taking warfarin (58%). Some of the other comorbidities associated with coagulopathy in our population included hepatic failure/cirrhosis in 4 patients, hematologic malignancy in 4 patients, and sepsis in 1 patient. Of these 9 patients with other comorbidities, 2 were receiving warfarin. We found that in coagulopathic patients that received FFP (38 patients) or vitamin K (35 patients), the median time until correction of coagulopathy was 29 hours (range 7–72 hours). The mean ICU and hospital LOSs in all pa-
patients were 3.7 ± 2.9 days and 8.4 ± 7.1 days, respectively. In the univariate analysis, there was no difference in the LOS between the coagulopathic versus noncoagulopathic patients for either the ICU or hospitalization (Table 2). The overall inhospital and 6–month mortality rates for patients with acute SDH were 5% and 23%, respectively. There was a significantly higher mortality rate in coagu-

Discussion

Our data indicate that coagulopathy was independently associated with increased inhospital death in our patients with acute SDH. This relationship was suggested in 2 previously reported case series.⁴,¹² One study evaluated neu-

Overall, our mortality rates were lower than what has been previously reported.¹¹,²³ This disparity may be due to the fact that our hospital is not a Level I trauma center and thus our patients may have had less severe brain injuries or lack of multiorgan trauma. This disparity may also be related to several other factors including neurosurgical expertise, the presence of a NICU team,²⁰ or a short time until surgery. In a study by Seelig and colleagues,¹⁰ the mortality rate of patients with traumatic acute SDH treated within 4 hours was 30%, compared with 90% when treatment occurred after 4 hours. Although we did not collect data regarding the mean time until treatment in our patients, the neurosurgeons at our institution generally operate as soon as it is feasible. It is possible that the coagulopathic patients received surgery later than patients with noncoagulopathic acute SDH pending correction of their coagulopathy, which may partially explain why coagulopathy is associated with a worse outcome.

Our finding that coagulopathy independently predicts a worse inhospital mortality rate is similar to the relationship found in OAT-associated spontaneous ICH.⁶,¹⁵,¹⁹ Ros-\n
The optimal treatment of hemorrhage associated with coagulopathy in various forms of intracranial hemorrhag-

e, including SDH and ICH, is a subject of controversy. The various treatment options include FFP, vitamin K, PCC, and rFVIIa.¹⁹ The prolonged time required for correction of coagulopathy using FFP and vitamin K in our study is likely suboptimal. Recombinant activated factor VIIa

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may achieve a quicker reversal of the INR, but whether this benefit will improve long-term outcomes is uncertain. Brody et al. reported using FFP and vitamin K to correct coagulopathy in patients with ICH with a median time to reversal of INR (< 1.3) of 32.2 hours; this time is similar to the median time to correction of the INR (29 hours) in our study. When patients received rFVIIa in addition to FFP and vitamin K, the median time to coagulopathy correction was significantly shorter (8.8 hours; p = 0.016). Likewise, Sorensen and associates reported rapid reversal of elevated INRs (range 1.7–6.6) in 7 patients with central nervous system bleeding to ≤ 1.5 within 10 minutes after a single dose of rFVIIa. Despite the potential for a quicker reversal of coagulopathy using rFVIIa, there are no large randomized controlled trials to support its current use on a routine basis for central nervous system hemorrhage. The Factor Seven for Acute Hemorrhagic Stroke (FAST) III trial that evaluated the efficacy of rFVIIa in patients with ICH was recently completed, and the preliminary results reported at the May 2007 American Academy of Neurology meeting did not support a benefit of rFVIIa in patients with ICH treated within 4 hours of symptoms. Prothrombin complex concentrate is another promising treatment alternative to FFP or rFVIIa that has been shown to rapidly correct an elevated INR. Additionally, anticoagulated rats that received either PCC or rFVIIa had significant reductions in INR, but only PCC-treated rats had reductions in partial thromboplastin time and bleeding time as well. One of the major limitations of our study is in its design. Because our analysis was a retrospective analysis, we cannot draw any firm conclusions regarding causality of coagulopathy on outcomes in patients with acute SDH; however, it is unlikely that this causality would be able to be tested in a prospective randomized manner due to ethical reasons. Another important issue is our definition of coagulopathy. The INR is a laboratory surrogate measure for clinical abnormalities in coagulation, but the exact level of INR at which coagulation is impaired clinically is debatable. We defined coagulopathy as an INR > 1.2 or PT ≥ 12.7 seconds because these values were considered abnormal in our laboratory (≥ 2 SDs above the mean). Also, at the time, the consensus among the neurointensivists and neurosurgeons at our institution was to correct coagulopathy to within the normal laboratory range. The

<table>
<thead>
<tr>
<th>Variable</th>
<th>Noncoagulopathic Patients (%)</th>
<th>Coagulopathic Patients (%)</th>
<th>p Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>age (yrs)</td>
<td>70 ± 16</td>
<td>75 ± 13</td>
<td>0.08</td>
</tr>
<tr>
<td>male</td>
<td>116 (61)</td>
<td>32 (60)</td>
<td>0.96</td>
</tr>
<tr>
<td>admission source</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>direct</td>
<td>24 (13)</td>
<td>7 (13)</td>
<td>reference value</td>
</tr>
<tr>
<td>ED</td>
<td>18 (9)</td>
<td>15 (28)</td>
<td>0.05</td>
</tr>
<tr>
<td>regular unit or other hospital</td>
<td>15 (8)</td>
<td>5 (9)</td>
<td>0.84</td>
</tr>
<tr>
<td>operating room</td>
<td>10 (5)</td>
<td>3 (6)</td>
<td>0.97</td>
</tr>
<tr>
<td>RR</td>
<td>121 (64)</td>
<td>22 (42)</td>
<td>0.33</td>
</tr>
<tr>
<td>other ICU</td>
<td>3 (2)</td>
<td>1 (2)</td>
<td>0.91</td>
</tr>
<tr>
<td>prior functional status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>independent</td>
<td>122 (64)</td>
<td>34 (64)</td>
<td>reference value</td>
</tr>
<tr>
<td>mild disability</td>
<td>44 (23)</td>
<td>15 (28)</td>
<td>0.28</td>
</tr>
<tr>
<td>moderate disability</td>
<td>23 (12)</td>
<td>2 (4)</td>
<td>0.02</td>
</tr>
<tr>
<td>severe disability</td>
<td>2 (1)</td>
<td>2 (4)</td>
<td>0.18</td>
</tr>
<tr>
<td>APACHE III score</td>
<td>42 (15–105)‡</td>
<td>54 (11–119)‡</td>
<td>&lt;0.001§</td>
</tr>
<tr>
<td>GCS score &lt; 8 on admission</td>
<td>26 (14)</td>
<td>15 (28)</td>
<td>0.01</td>
</tr>
<tr>
<td>using mechanical ventilation</td>
<td>31 (16)</td>
<td>14 (26)</td>
<td>0.09</td>
</tr>
<tr>
<td>treatment for acute SDH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nonop</td>
<td>57 (30)</td>
<td>25 (47)</td>
<td></td>
</tr>
<tr>
<td>op</td>
<td>134 (70)</td>
<td>28 (53)</td>
<td>0.03</td>
</tr>
<tr>
<td>ICU discharge disposition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>regular unit</td>
<td>170 (89)</td>
<td>47 (89)</td>
<td>reference value</td>
</tr>
<tr>
<td>death</td>
<td>9 (5)</td>
<td>4 (8)</td>
<td>0.4</td>
</tr>
<tr>
<td>other ICU transfer</td>
<td>2 (1)</td>
<td>1 (2)</td>
<td>0.6</td>
</tr>
<tr>
<td>home</td>
<td>7 (4)</td>
<td>0</td>
<td>0.2</td>
</tr>
<tr>
<td>nursing facility</td>
<td>3 (2)</td>
<td>1 (2)</td>
<td>0.9</td>
</tr>
<tr>
<td>ICU LOS (days)</td>
<td>4 ± 3</td>
<td>4 ± 4</td>
<td>0.39</td>
</tr>
<tr>
<td>hospital LOS (days)</td>
<td>8 ± 7</td>
<td>9 ± 7</td>
<td>0.69</td>
</tr>
<tr>
<td>hospital discharge disposition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>home</td>
<td>107 (56)</td>
<td>19 (36)</td>
<td>reference value</td>
</tr>
<tr>
<td>nursing facility</td>
<td>60 (32)</td>
<td>20 (38)</td>
<td>0.08</td>
</tr>
<tr>
<td>other hospital</td>
<td>8 (4)</td>
<td>1 (2)</td>
<td>0.74</td>
</tr>
<tr>
<td>death</td>
<td>16 (8)</td>
<td>13 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>withdrawal of support</td>
<td>12 (6)</td>
<td>8 (15)</td>
<td>0.04</td>
</tr>
<tr>
<td>death at 6 months</td>
<td>39 (20)</td>
<td>17 (32)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

* 191 patients without coagulopathy (defined as having a PT < 12.7 seconds or INR ≤ 1.2) versus 53 coagulopathic patients (defined as having a PT ≥ 12.7 seconds or INR > 1.2).† Unless otherwise indicated, probability value obtained using the chi-square test or student t-test.‡ Median and range.§ Probability value obtained using the Mann–Whitney U-test.
INR threshold of 1.2 has been used previously in clinical trials. The Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial evaluated the addition of clopidogrel, simvastatin, or both to aspirin monotherapy after hyperacute stroke, and excluded patients with INR > 1.2. Additionally, a randomized trial testing a recombinant form of tissue factor in the setting of severe sepsis stratified patients by “low INR (< 1.2)” or “high INR (> 1.2)” (1). Hopefully, future randomized controlled trials evaluating strategies for the correction of coagulopathy in neurosurgical patients will elucidate the optimal INR target.

Furthermore, the manner in which the FFP and vitamin K were administered was not standardized. It is possible that if these had been administered in a standardized fashion, the relationship between coagulopathy and inpatient outcomes may have been attenuated. However, the duration of time required to correct coagulopathy in this study was similar to that reported in the literature. Also, we did not specifically explore the relationship between antiplatelet agents and acute SDH as this information was not easily obtainable in the medical records. It would be of interest to know if the presence of antiplatelet use also independently predicted a worse outcome in patients with acute SDH, as it is common practice to reverse platelet dysfunction with platelet transfusions in these patients if a history of antiplatelet agent use is obtained. Additionally, the most common cause of inpatient death was withdrawal of mechanical ventilation. Although this most likely was a consequence of massive brain injury with impending brain death or a high likelihood of severe neurological outcome, we cannot always prognosticate outcomes with a high degree of accuracy. Therefore, it is possible that some of the patients underwent withdrawal of mechanical support would have survived beyond hospitalization and thus the apparent relationship between acute SDH and inpatient death would be attenuated.

Another limitation of the study is the lack of initial imaging data (such as a head CT scan) to evaluate the relationship between acute SDH volume and midline shift with clinical outcome. Also, we found that coagulopathy was associated with inpatient death, and although there was a trend for long-term death, it did not reach statistical significance. It is possible that if our sample size had been larger such a statistical difference would have been achieved. In addition, we did not have data on long-term quality of life or disability. Finally, our study was not sufficiently powered to determine whether the mortality rate was related to the time of correction of coagulopathy. In a recent study evaluating factors associated with successful reversal of INR in warfarin-associated ICH, Goldstein and colleagues (9) reported that a shorter time until administration of FFP and vitamin K was the most important indicator of successful reversal of INR within 24 hours in patients with warfarin-associated ICH; however, it was not associated with lower morbidity or mortality rates. A prospective randomized trial is needed to determine whether prompt correction of coagulopathy with various blood products and/or vitamin K improves outcomes.

Conclusions

In a large series of patients with acute SDH, only APACHE III scores and coagulopathy were independently associated with increased inhospital deaths. The time until correction of coagulopathy using FFP and/or vitamin K was prolonged. There is a need for a prospective randomized trial comparing different modalities of coagulopathy correction in patients with acute SDH.

Disclaimer

The authors do not report any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References


* Adjusted for age, admission source, prior functional status, and withdrawal of support.

### TABLE 3

Predictors of inhospital death from the logistic regression model

<table>
<thead>
<tr>
<th>Covariates</th>
<th>OR</th>
<th>95% CIs</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>APACHE III score</td>
<td>4.4</td>
<td>1.4–13.4</td>
<td>0.011</td>
</tr>
<tr>
<td>coagulopathy</td>
<td>2.7</td>
<td>1.1–7.1</td>
<td>0.037</td>
</tr>
<tr>
<td>surgical evacuation</td>
<td>0.2</td>
<td>0.1–0.6</td>
<td>0.003</td>
</tr>
</tbody>
</table>

### References

Coagulopathy in subdural hematoma


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