PERIOPERATIVE ASSESSMENT OF COAGULABILITY IN NEUROSURGICAL PATIENTS USING THROMBOELASTOGRAPHY

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BACKGROUND
Thrombelastography is a useful technique for evaluating coagulability. We hypothesized that it could be used to determine postoperative hematologic complications during and after neurologic surgery.

METHODS
Forty-six neurosurgical patients were stratified by diagnosis: subarachnoid hemorrhage from ruptured intracranially aneurysms, intracranial-axial lesions, intracranial-extra-axial lesions, and degenerative spine disease. Thromboelastograms were performed before, during, and after surgery. Hematologic data were collected preoperatively and postoperatively; computed tomography scans and lower extremity Doppler sonography were performed postoperatively. A thrombosis index (TI) was used to assess coagulability.

RESULTS
Coagulability increased over the course of surgery for all patients ($p < 0.0001$). In craniotomy patients, coagulability increased over the course of surgery ($p < 0.05$) with the most dramatic increase from intubation to skin incision ($p < 0.05$), and then after tumor removal or aneurysm clipping ($p < 0.10$). Univariate analysis among craniotomy patients showed that female gender ($p < 0.0004$) and smoking ($p < 0.06$) were associated with hypercoagulability. Among craniotomy patients, younger age was associated with hypercoagulability in the preoperative period ($p < 0.01$). There was no significant association between coagulability and aspirin or NSAID use, or intraoperative fluid volume. No patient developed a postoperative hematoma and one patient (2.2%) developed a lower extremity deep vein thrombosis.

CONCLUSIONS
Increased coagulability begins between induction of anesthesia and skin incision, and continues to increase throughout surgery. These changes are more pronounced in patients undergoing craniotomy compared to patients undergoing spine procedures. © 2002 by Elsevier Science Inc.

KEY WORDS
Blood coagulation, coagulability, deep vein thrombosis, thromboelastography.

Thrombelastography (TEG) is a technique that allows for global assessment of hemostatic function using a patient’s blood to determine the interaction between platelets and the coagulation cascade. In particular, TEG assesses coagulation from primary hemostasis through fibrinolytic activity by measuring the shear elastic modulus (dynes per centimeter squared) during clot formation in whole blood [6,7,9]. Thromboelastography can provide information on coagulation factor deficiencies, platelet function, and fibrinolysis, and has the advantage over traditional coagulation tests of correlating with blood loss [18]. It has been shown to be useful in predicting which patients will require a transfusion and identifying those craniotomy patients at high risk for postoperative hematomas [5,9,14]. In previous studies, TEG has successfully detected early coagulopathies and intraoperative coagulation defects, and reduced the number of blood transfusions in transplant, cardiac, and trauma surgery [8,11,16,17].

In this study, we compared thromboelastographic profiles of neurosurgical patients undergoing craniotomy for aneurysm or tumor to those of patients undergoing spine surgery. We hypothe-
sized that TEG would identify temporal changes in coagulability throughout surgery, and correlate with those patients developing postoperative hematomas or deep vein thromboses.

**Patients & Methods**

**Patients**
The protocol was reviewed and approved by the Internal Review Board at the Hospital of the University of Pennsylvania. Patients undergoing craniotomy or spine surgery were entered into the study; patients undergoing emergency procedures and those with significant co-morbidities were excluded. Patients were stratified into four diagnosis groups: subarachnoid hemorrhage because of ruptured cerebral aneurysm (SAH), intracranial-intra-axial lesions (IAL), intracranial-extra-axial lesions (EAL), and patients undergoing spine surgery (Spine), who served as a control group. Other patient data that were collected included use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs), a history of smoking, and total intraoperative fluid volume. Preoperative and postoperative hematologic data included prothrombin time (PT), partial thromboplastin time (PTT), platelet count, and hematocrit (HCT). Fibrinogen, thromboplastin time (TT), fibrin split products (FSP), D-dimer, and Factor VII levels were also obtained postoperatively. On the first postoperative day, craniotomy patients were evaluated with computed tomography (CT) scans of the head. All patients were evaluated with lower extremity Doppler sonography at 1 week after surgery.

**Thromboelastography**

To obtain a thromboelastogram, whole blood (about 0.5 mL) is placed into a heated cup and a pin suspended by a torsion wire is lowered into the blood sample (Figure 1). The pin is oscillated and as the blood begins to clot, torque gradually increases on the wire and is recorded. An increase in the R (normal range: 6–8 min) can occur with coagulation factor deficiencies or anticoagulation whereas a decrease can represent a hypercoagulable state. The K (normal range: 3–6 min) is the coagulation time and reflects the activity of the intrinsic clotting factors, fibrinogen, and platelets. The alpha angle (normal range: 50–60°, e.g.) is a measure of the speed of solid clot formation where decreases in the angle may be because of hypofibrinogenemia and thrombocytopenia. The maximum amplitude (MA) (normal range: 50–60 mm) of the thromboelastograph determines the

![Thromboelastogram](https://via.placeholder.com/150)

**Figure 1** Principles of thromboelastography. Whole blood is placed into a heated cup and a pin suspended by a torsion wire is lowered into the cup. The pin is oscillated and as the blood begins to clot, torque gradually increases on the wire and is recorded.

\[
TI = -0.1227R + 0.0092K + 0.1655MA - 0.0241\alpha - 5.022
\]

The TI reflects the interaction of the clotting cascade and overall platelet function in whole blood rather than the traditional manner of using the PT and PTT. The reported normal range for this index is \(-2 \leq TI \leq +2\) with a more positive value reflecting hypercoagulability and a more negative value reflecting hypocoagulability [10]. The physical characteristics of clot formation were measured by TEG using a thromboelastogram coagulation analyzer (Hemoscope; Skokie, IL). Indices of clot formation (R, K, MA, and \(\alpha\), A60) were measured and TI was calculated using the above equation.

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strength of the clot and may be reduced with abnormal fibrin or platelet function.

In this study, blood samples were obtained while the patient was in the operating room by the anesthesiologist and thromboelastograms were obtained by a thromboelastogram coagulation analyzer in the operating room itself. Thromboelastograms were obtained at three time points throughout surgery: before the induction of anesthesia while the patient was in the operating room, after skin incision, and after closure of the skin incision. In those patients undergoing craniotomy, another thromboelastogram was obtained after aneurysm clipping or removal of the intra-axial or extra-axial lesion. Thromboelastogram parameters (R, K, α, MA, and A60) were recorded for each patient at each time point and collected in a spreadsheet.

STATISTICAL ANALYSIS

Differences in intraoperative fluid volume were examined using one-way analysis of variance with a Tukey approach to the multiple comparisons. Thromboelastogram data were collected and a repeated measures analysis of variance (ANOVA) was used to determine whether: 1) mean TI changed over surgery (time effects), 2) mean TI was associated with individual predictor variables (gender, diagnosis, age, aspirin, NSAIDs, smoking, and intraoperative fluid volume) (group effects), and 3) individual predictors were associated with differences in mean TI over the course of surgery (group-time interactions). Since spine patients were evaluated with three surgical time points and craniotomy patients were evaluated using four, two separate analyses were performed. A multivariate approach using Hotelling’s T2 was used to examine differences between mean TI at pairs of time points. Statistical analyses were done using statistical software, SAS 6.0 and S-PLUS (Mathsoft, Cambridge, MA).

RESULTS

Forty-eight consecutive patients were enrolled in the study; no measurements were recorded for one patient and a second spine patient who had missing data for the postoperative time point was also omitted from the study. Analyses were performed using 46 patients, 26 male and 20 female, with ages ranging from 17 to 81 years with a mean age of 48 years (Table 1). The SAH group consisted of 10 patients (22%) diagnosed with intracranial (IC) aneurysms who underwent a craniotomy for surgical clipping. The IAL group consisted of 22 patients (48%) with 5 metastatic, 15 primary glioblastoma, and 2 diffuse parenchymal lesions. The EAL group consisted of 4 patients (8%) with two meningiomas, one epidermoid, and a pituitary adenoma. The spine group consisted of 10
patients (22%) undergoing surgery for cervical or lumbar degenerative disease. Data on aspirin and NSAID usage and smoking were available for 45 patients. Seventeen patients (38%) were taking aspirin, 24 patients (53%) were taking NSAIDs, and 26 patients (56%) had a positive history of smoking.

Preoperative and postoperative hematologic profiles were obtained and stratified by study group (Table 2 and 3). The profiles among these groups were similar. Analysis of variance indicated that patients with IAL received significantly lower volumes of fluid than any other group \( (p < 0.003) \) (Table 2). No patient developed a postoperative hematoma that required surgery. One patient (2.2%) from the IAL group developed a lower-extremity deep vein thrombosis that required treatment.

### ALL PATIENTS

For all patients, mean TI increased significantly over the course of surgery from \(-0.67\) preoperatively to \(1.33\) postoperatively \( (p < 0.0001) \). Univariate repeated measures ANOVA showed that differences in mean TI between males and females was highly significant \( (p < 0.0001) \) (Table 4). For all patients, there was no significant association between mean TI and aspirin use, NSAID use, or intraoperative fluid volume (Table 4).

When comparing coagulability in craniotomy and spine patients, the two groups differed overall \( (p < 0.08) \) and over time \( (p < 0.06) \) (Table 4). Preoperatively, both craniotomy and spine patients were initially hypocoagulable \( (\text{mean TI} = 0.66 \text{ vs. } 0.82) \); however, by the postoperative period TI had increased in both groups with craniotomy patients tending to be more hypercoagulable than spine patients \( (\text{mean TI} = 1.63 \text{ vs. } 0.03) \) \( (p < 0.04) \) (Table 5). For craniotomy patients, there was a significant increase in coagulability from intubation to skin incision \( (0.66 \text{ vs. } 0.62) \) \( (p < 0.05) \) and a marginal increase in coagulability from skin incision to tumor removal or aneurysm clipping \( (0.62 \text{ vs. } 1.23) \) \( (p < 0.10) \) (Table 5). There was no significant difference from the time of tumor removal or aneurysm clipping to the period after extubation \( (1.23 \text{ vs. } 1.63) \). Differences between pairs of consecutive time peri-

### Perioperative Hematologic Profiles, Postoperative Hematological Profiles, and Total Intraoperative Fluid Volume by Diagnosis Group [mean (standard deviation)]

<table>
<thead>
<tr>
<th></th>
<th>PT (SEC)</th>
<th>PTT (SEC)</th>
<th>HCT (%)</th>
<th>PLATELETS (×10³ ML)</th>
<th>VOLUME (ML)</th>
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<tr>
<td><strong>SAH (n = 10)</strong></td>
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<tr>
<td>Pre-op</td>
<td>12.5 (1.4)</td>
<td>24.2 (4.2)</td>
<td>38.6 (3.4)</td>
<td>226.5 (59.5)</td>
<td>2210 (1198)</td>
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<td>Post-op</td>
<td>12.7 (0.5)</td>
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<td>31.7 (3.6)</td>
<td>201.2 (62.8)</td>
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<tr>
<td><strong>IAL (n = 22)</strong></td>
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<td>897 (1043)</td>
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<td>12.2 (0.5)</td>
<td>23.2 (2.7)</td>
<td>40.6 (4.1)</td>
<td>245.9 (54.7)</td>
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<tr>
<td>Post-op</td>
<td>12.5 (0.4)</td>
<td>21.0 (2.5)</td>
<td>37.3 (4.4)</td>
<td>240.3 (56.5)</td>
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<td><strong>EAL (n = 4)</strong></td>
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<td>39.5 (11.1)</td>
<td>246.5 (95.7)</td>
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<td>36.0 (4.1)</td>
<td>231.7 (88.9)</td>
<td>2975 (2254)</td>
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<tr>
<td><strong>Spine (n = 10)</strong></td>
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<td>2235 (1310)</td>
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<td>40.5 (3.2)</td>
<td>224.3 (40.3)</td>
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<tr>
<td>Post-op</td>
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<td>35.5 (4.2)</td>
<td>195.2 (23.5)</td>
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<tr>
<td><strong>All Patients (n = 46)</strong></td>
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<td>1654 (1434)</td>
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<tr>
<td>Pre-op</td>
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<td>24.0 (3.0)</td>
<td>40.0 (4.6)</td>
<td>237.3 (56.4)</td>
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<tr>
<td>Post-op</td>
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<td>22.7 (3.3)</td>
<td>35.6 (4.6)</td>
<td>222.4 (58.7)</td>
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</tr>
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</table>
ods for the spine group were not statistically significant.

**CRANIOTOMY PATIENTS**

We next excluded spine patients from the analysis and considered differences among craniotomy patients. (Table 5). Patients with EALs were particularly hypercoagulable with mean TI levels above the normal range after tumor removal and extubation (mean TI = 2.31–2.34). However the results of a second repeated measures ANOVA did not indicate any statistical evidence of differences among groups (p = 0.27, p = 0.57) (Table 4). There were significant differences in coagulability between males and females (p < 0.004), and also an effect from smoking (p < 0.06). Overall, smokers tended to be hypercoagulable, and there was also a significant difference in preoperative coagulability between smokers and non-smokers (p < 0.05). Lastly, when age was examined as a continuous variable it was found to significantly affect coagulability over the course of surgery (p < 0.01). There was no significant association between coagulability and aspirin use, NSAID use, or intraoperative fluid volume.

**MULTIVARIABLE MODELS**

In a statistical model comparing coagulability in craniotomy to spine patients while adjusting for gender, we continued to find a strong effect of gender (p < 0.0001). In addition, the evidence of different patterns of coagulability over time in craniotomy versus spine patients was slightly stronger in the multivariable model (p = 0.054) compare to the univariate model (p = 0.062) (Table 4). In a statistical model comparing coagulability in smokers versus non-smokers while adjusting for gender, we continued to find a strong effect of gender (p < 0.0003). However, there was no longer a significant effect of smoking (p < 0.16). In a statistical model comparing coagulability in older (>52 years) versus younger (<52 years) patients while adjusting for gender, we continued to find a strong effect of gender (p < 0.0004) and a marginal effect of age (p < 0.09).

**DISCUSSION**

In this study, we used TEG to assess coagulability in neurosurgical patients before, during, and after surgery. No patient developed a postoperative hema-
Thromboplastin (tissue factor) is abundantly stored in the brain and released after head injury or IC surgery thus contributing to the hypercoagulability that may develop in these patients [12,13]. Thromboplastin activates the extrinsic pathway of the coagulation cascade causing thrombin formation and subsequent fibrin deposition. As such, one would expect the greatest change in coagulability to be from skin incision to tumor removal or aneurysm clipping when there is the most brain manipulation, especially in intra-axial lesions. However, our results showed that craniotomy patients had the most significant increase in coagulability from induction of anesthesia to skin incision and a marginal increase in coagulability during brain manipulation. The reasons for this change are not clear and most likely are because of anesthetic agents administered during induction. Fluid volume would dilute coagulation factors, causing a relative hypo-coagulable state, and this was not the case in our patients.

Although not statistically significant, we observed that patients in the IAL group who would have the most brain manipulation and thromboplastin release during tumor removal actually had minimal change in coagulability compared to other craniotomy groups. Surprisingly, the EAL group had the most change in coagulability during brain manipulation (mean increase in Ti = 1.66) followed by the SAH group (mean increase in Ti = 0.71) and lastly, the IAL group. Our results for Ti by group are counterintuitive to the current thought that brain retraction increases thromboplastin release with subsequent enhanced clot formation. However, this conclusion is limited since only four patients were in the EAL group, making it difficult to compare with the IAL group (n = 22). Typically at our institution, patients undergoing neurosurgery have pneumatic compression boots placed after intubation to prevent any possibility of thrombotic complications from venous pooling. However, our data suggest that the coagulation cascade may be initiated before brain manipulation and that devices to prevent lower extremity DVTs, such pneumatic compression boots, should be placed before induction of anesthesia. Additional study of the temporal changes in TEG after induction could determine the course of this increase in coagulability.

Intraoperative fluid volume could also contribute to changes in coagulability. Brain tumor patients would be expected to be fluid negative and hypercoagulable, whereas aneurysm patients would be
expected to be fluid positive and hypocoagulable. In our study IAL patients were relatively hypovolemic compared to other groups, and somewhat surprisingly, EAL patients relatively hypervolemic. There was no significant correlation between intraoperative fluid volume and either mean coagulability or coagulability changes over the course of surgery. Also, patients tended toward hypercoagulability in the postoperative period rather than hypocoagulability, contrary to the expected dilutional coagulopathy secondary to excess volume.

**CONCLUSION**

Thromboelastography is a simple, useful technique for evaluating coagulability in patients undergoing neurosurgical procedures. Our results showed that coagulability begins with induction of anesthesia and increases through the course of surgery, with the most dramatic increases during the early stages. In this cohort, younger, female patients who underwent craniotomy were the most hypercoagulable and possibly at a greater risk for thrombotic complications. Changes in TI over the course of surgery and the rate of change may be important risk factors in assessing coagulability and challenge the thromboplastin theory. Further studies are warranted to determine whether TEG can predict thrombotic and hemorrhagic complications in neurosurgical patients.

*We thank Christine Hardy for preparing many of the descriptive analyses.*

**REFERENCES**


**COMMENTARY**

The authors evaluate coagulation characteristics in neurosurgical patients, including those with subarachnoid hemorrhage, extra-axial and intra-axial cranial lesions, and spinal surgery. They have found that progressive hypercoagulability occurred over the course of surgery in all patients. Gender and smoking were associated with hypercoagulability as well. Young age is also associated with hypercoagulability preoperatively. Outcomes, in terms of the specific coagulation issues of deep vein thrombosis and postoperative hematoma, occurred at the statistically expected incidence across all groups.

This report by Abrahams et al adds significantly to the literature regarding coagulation in neuro-