

Hemostatic Changes in Pediatric Neurosurgical Patients as Evaluated by Thrombelastograph[®]

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Thromboembolic events are a known complication in neurosurgical patients. There is evidence to suggest that a hypercoagulable state may develop perioperatively. Thrombelastograph[®] (TEG[®]) coagulation analysis is a reliable method of evaluating hypercoagulability. We evaluated coagulation by using TEG[®] data in pediatric neurosurgical patients undergoing craniotomy to determine whether a hypercoagulable state develops intraoperatively or postoperatively. Thirty children undergoing craniotomy for removal of a tumor or seizure focus were studied. Blood was analyzed with TEG[®] data by using native and celite techniques, at three time points for each patient: preoperatively after induction of anesthesia; intraoperatively during closure of the dura; and on the first postoperative day.

Compared with preoperative indices, closing and postoperative celite TEG[®] values were indicative of hypercoagulability with shortened coagulation time values ($P < 0.001$), prolonged α angle divergence values ($P < 0.001$), and above-normal TEG[®] coagulation indices ($P \leq 0.002$). Reaction time values were shortened, and maximal amplitude of clot strength values were prolonged but did not reach statistical significance. Hypercoagulation develops early after resection of brain tissue in pediatric neurosurgical patients as assessed by using TEG[®] data. Further studies are needed to determine the clinical significance of this hypercoagulable state.

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Thromboembolic events, such as deep venous thromboses (DVT) and pulmonary emboli (PE), are known postoperative complications in neurosurgical patients. In addition to risk factors including malignancy, trauma, and immobility, there is evidence to suggest that a hypercoagulable state may develop intraoperatively or postoperatively (1). Perioperative thrombosis occurs in 10%–43% of neurosurgical patients and PE is implicated in 3% of neurosurgical deaths in the adult population (2). In the pediatric population, 13% of all cases of venous thromboembolism are associated with surgery (3). The incidence associated with pediatric neurosurgery is ill defined and merits further investigation.

Intracranial surgery is associated with an increased incidence of coagulation disorders (thrombosis and

thromboembolism) compared with general surgical procedures (4,5). It is thought that the incidence of coagulation abnormalities in patients having intracranial surgery is related to the severity or extent of brain tissue injury, being more frequent in patients having more extensive surgery (5,6).

Previous investigators have shown activation of the hemostatic system after intracranial surgery by using various hemostatic studies. Postoperative activated partial thromboplastin time (aPTT) was shortened and bleeding time reduced in one study in neurosurgical patients (4). Other investigators have shown that increases in the following markers of coagulation occur perioperatively: fibrin and fibrin degradation products (4), thrombin antithrombin III complex, plasmin α_2 -antiplasmin complex, β -thromboglobulin, fibrinogen, and platelet factor 4 levels (7).

Thrombelastograph[®] (TEG[®]) coagulation analysis (Haemoscope Corporation, Skokie, IL) provides a method for evaluation of the coagulation system from initial clot formation to clot retraction or dissolution. TEG[®] analysis is very sensitive in the identification and measurement of hypercoagulability, which cannot be detected by routine laboratory tests (8,9). TEG[®] analysis is already being used in the diagnosis and

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treatment of coagulopathies associated with liver transplantation (10) and cardiac surgery (11).

One study using TEG[®] data to evaluate hemostatic changes during neurosurgery in adult patients with primary brain tumors demonstrated a hypercoagulable state intraoperatively and in the immediate postoperative period (12). Prothrombin (PT) and aPTT values did not change significantly, indicating that TEG[®] coagulation analysis may be a more sensitive measure of hypercoagulability. However, there have not been any studies using TEG[®] data to assess changes in hemostasis in pediatric patients having neurosurgical procedures. The purpose of this study was to evaluate coagulation by using TEG[®] data in pediatric neurosurgical patients undergoing craniotomy and to determine whether a hypercoagulable state is present or develops perioperatively.

Materials and Methods

After IRB approval and informed consent from the patient and/or their parents, children presenting for intracranial surgical procedures involving brain resection for removal of a tumor or seizure focus were evaluated. Exclusion criteria included all patients with acute trauma, intracranial bleeding, or a known coagulation disorder.

Demographic data such as patient age, diagnosis, coexisting disease state(s), operation planned, and preoperative medications (including anticonvulsant and/or nonsteroidal antiinflammatory medications) were documented. Routine blood values including hemoglobin, hematocrit, platelet count, PT, aPTT, liver function tests, and anticonvulsant levels were recorded. All patients had a standard anesthetic consisting of a premedicant of midazolam, induction with sevoflurane by inhalation or IV with thiopental, and maintenance with fentanyl, pancuronium, nitrous oxide, and isoflurane. An arterial catheter was placed routinely for the surgery. Intraoperative blood loss was estimated by using standard clinical variables (blood in suction containers and weight of sponges). Blood and blood product transfusions were recorded if administered. The amount of brain resected was categorized as focal resection, lobectomy, or hemispherectomy. The duration of surgery was also recorded.

Three blood samples were obtained from the arterial catheter and analyzed by using TEG[®] data: after induction of anesthesia before the surgical incision (pre), at the end of the procedure before emergence from anesthesia (intraop), and the morning of postoperative Day 1 (postop).

The method of collection was standardized. Each sample was obtained by using a two-syringe technique through a port located at the hub of the arterial catheter near the entry site. After aspiration, and discarding 10 mL of blood to avoid contamination by the

arterial flush solution, a second sample of 2 mL was withdrawn and used for TEG[®] measurements. All TEG[®] samples were made at 37°C using disposable plastic cups and pins by a computerized Thrombelastograph Coagulation Analyzer (Model 3000; Haemoscope). Both native and celite techniques were run for each sample. The native technique consisted of using 360 μ L of whole blood assayed 4 min after obtaining the sample. Celite-activated samples were assayed by using 1 mL of whole blood placed in a 1% celite vial containing 90 μ L of celite particles and mixed thoroughly by inversion 5 times. A 360- μ L aliquot was then pipetted and analyzed 4 min after obtaining the sample. Mineral oil was spread over the blood surface to prevent evaporation. The TEG[®] analyzer was allowed to run until LY60 (lysis at 60 min; reduction in the maximal amplitude of the TEG[®] tracing after 60 min) could be determined.

Four indices of clot formation were measured on the TEG[®] analyzer: R time (reaction time to clot formation), K time (coagulation time, time to achieve clot strength), MA (maximal amplitude of clot strength), and α angle (angle of divergence, rate of clot growth). The TEG[®] coagulation index (CI), derived from a linear equation that combines all the TEG[®] variables (see Appendix), was also calculated.

Differences between preoperative, intraoperative, and postoperative TEG[®] values were compared for native and celite sampling techniques separately. Repeated-measures analysis of variance (ANOVA) using the Greenhouse-Geisser F-test (13) adjusting for significant covariates (hematocrit, platelets, and fibrinogen) followed by simple contrasts was performed to compare TEG[®] indices between time points using the SPSS statistical package (Version 9.0; SPSS Inc., Chicago, IL). To account for the three time points, a Bonferroni-corrected value of $P < 0.017$ (obtained by dividing 0.05 by 3) was used as the criteria for statistical significance. Power analysis using nQuery Advisor (version 3.0; Statistical Solutions, Boston, MA) indicated that 30 patients would provide more than 95% power to detect an effect size of 1.0 (difference of 1 standard deviation) between preoperative, intraoperative, and postoperative time points in each of the 5 outcome variables (R time, K time, MA, α angle, and CI). ANOVA data analysis using the Greenhouse-Geisser F-test for between subject effect was used to determine differences in TEG[®] variables between patients who received a blood transfusion and those that did not. Unpaired Student *t*-tests were used to determine differences in TEG[®] variables between patients who had focal resections and those who underwent lobectomy and hemispherectomy. Normality was assessed by the Kolmogorov-Smirnov test, and none of the TEG[®] parameters showed significant departures from a Gaussian-shaped distribution. Data are presented as mean \pm SD and all *P* values are two-tailed.

Results

Thirty patients were enrolled in the study. Demographic and clinical data are shown in Table 1. All patients on anticonvulsant medications had levels within therapeutic range. No patients were taking nonsteroidal antiinflammatory medications for at least 2 wk before surgery.

Standard preoperative blood work was within normal limits in all except three patients. One patient (on phenobarbital) had a preoperative hematocrit of 25 with a normal PT, PTT, and platelet count; the corresponding preoperative TEG[®] variables showed a CI of 2.9 for native and 5.3 for celite techniques (normal range, -2.0 to 2.0). Another patient (on Dilantin[®]) had a preoperative hematocrit of 25 with a PTT of 18; this patient's preoperative CI was 2.3 and 5.0 for native and celite techniques, respectively. A third patient (on valproate) had a preoperative hematocrit of 28 and a PTT of 18; the preoperative CI was -1.6 (native) and -2.9 (celite).

Preoperative TEG[®] indices were all within normal limits except for five patients (including the three previously mentioned). Three patients had CIs more than 2 indicating preexisting hypercoagulability, and two patients had values less than -2 indicating hypocoagulability.

Estimated blood loss was <10% total blood volume in all cases except for six patients (three were focal resections, two hemispherectomies, one lobectomy); all six received an intraoperative blood transfusion. One hemispherectomy patient lost 200% of the estimated blood volume and was the only one who received additional blood products, including fresh frozen plasma and platelets. All resections were focal, except for the two lobectomies and three hemispherectomies.

TEG[®] data for the native and celite techniques are shown in Tables 2 and 3, respectively. With respect to the celite data, R values were higher for preoperative values (10.9 ± 4.0 mm) compared with intraoperative (8.2 ± 3.1 mm) and postoperative values (8.7 ± 3.1 mm), but did not reach significance. K values were higher for preoperative values (3.8 ± 1.7 mm) compared with intraoperative (2.7 ± 1.0 mm) and postoperative (3.0 ± 0.73 mm), and reached significance ($P < 0.001$ for both). The MA preoperatively (65.4 ± 7.7 mm) was less compared with intraoperative (67.5 ± 7.2 mm) and postoperative (66.9 ± 5.8 mm), but this did not reach significance. The α angle also increased when intraoperative (72.4 ± 5.5 degrees) and postoperative (71.1 ± 4.9 degrees) values were compared with preoperative values (66.3 ± 7.8 degrees) ($P < 0.001$ for both). Average CI preoperatively was 1.0 ± 2.3 whereas CI at intraoperative was 2.7 ± 1.8 and postoperatively was 2.4 ± 1.6 ($P < 0.001$ and $P =$

Table 1. Demographic and Clinical Data ($n = 30$)

Age (yr)	11 \pm 7
Male/female ratio	19/11
Patients on anticonvulsant medications	13 (43%)
Preoperative bloodwork	
Hematocrit (32.3%–44.8%)	37.3 \pm 6.1
Platelet count ($168\text{--}376 \times 1000/\text{mm}^3$)	280 \pm 115
PT (10.0–12.5 s)	11.6 \pm 0.7
aPTT (25.0–36.0 s)	26.4 \pm 4.6
Fibrinogen (200–400 mg/dL)	319 \pm 154
Duration of surgery (h)	6.3 \pm 2.4
Diagnosis	
Seizure surgery	13 (43%)
Tumor resection	17 (57%)
Type of brain resection	
Focal	25 (83%)
Lobectomy	2 (7%)
Hemispherectomy	3 (10%)

Values are means \pm SD or n (%).

PT = prothrombin time, aPTT = activated partial thromboplastin time.

0.002, respectively). No differences were detected between intraoperative and postoperative values for any of the TEG[®] variables. Samples collected by native technique showed a similar trend but did not reach significance for any of the TEG[®] variables between any time points.

No evidence of a postoperative clinical coagulopathy (DVT or PE) was observed on routine history and physical examinations in any patient during hospitalization. Data analysis using ANOVA F-tests for between subject effect did not reveal significant differences between those six patients who received a blood transfusion compared with those who did not ($P > 0.1$). Data analysis using unpaired Student's t -tests did not reveal significant differences regarding TEG[®] variables during more extensive brain resections (lobectomy and hemispherectomy) to those obtained for focal resections ($P > 0.1$).

Discussion

This study demonstrates that hypercoagulation develops after resection of brain tissue in pediatric patients as assessed by TEG[®]. The coagulation changes occurred in pediatric patients postcraniotomy. A cause-effect relationship can only be speculated. This trend was observed to begin intraoperatively and persisted into the first postoperative day. We did not find any relation between the amount of brain resected and the degree of hypercoagulation, perhaps because of the small number of patients having more than a focal resection. A number of uncontrolled variables, including temperature and hydration status, could have affected the results. This study was limited to postoperative Day 1; therefore, the duration to which TEG[®] value changes extend into the postoperative period is unknown.

Table 2. Preoperative, Intraoperative, and Postoperative Values for Native Technique

TEG [®] variable	Preop	Intraop	Postop	Preop versus intraop (P value)	Preop versus postop (P value)	Intraop versus postop (P value)
R (mm)	35.4 ± 14.2	34.0 ± 14.3	30.5 ± 12.2	0.62	0.08	0.30
K (mm)	14.6 ± 7.0	13.9 ± 4.9	11.8 ± 5.3	0.44	0.02	0.17
MA (mm)	55.3 ± 9.0	55.4 ± 7.9	58.3 ± 10.2	0.96	0.95	0.15
α angle (degrees)	33.1 ± 13.9	33.3 ± 10.1	33.3 ± 15.0	0.64	0.04	0.07
CI	-0.82 ± 2.5	-0.65 ± 2.2	-0.65 ± 2.2	0.50	0.04	0.17

Plus-minus values are means ± sd.

No statistically significant differences based on Bonferroni-corrected $P < 0.017$ were found for any of the TEG[®] variables.

TEG[®] = thrombelastograph, preop = preoperative, intraop = intraoperative, postop = postoperative, R = reaction time to clot formation, K = coagulation time, MA = maximum amplitude of clot strength, α angle = angle of divergence, CI = coagulation index.

Table 3. Preoperative, Intraoperative, and Postoperative Values for Celite Technique

TEG [®] variables	Preop	Intraop	Postop	Preop versus intraop (P value)	Preop versus postop (P value)	Intraop versus postop (P value)
R (mm)	10.9 ± 4.0	8.2 ± 3.1	8.7 ± 3.1	0.23	0.8	0.45
K (mm)	3.8 ± 1.7	2.7 ± 1.0	3.0 ± 0.7	<0.001 ^a	<0.001 ^a	0.29
MA (mm)	65.4 ± 7.7	67.5 ± 7.2	66.9 ± 5.8	0.15	0.64	0.88
α angle (degrees)	66.3 ± 7.8	72.4 ± 5.5	71.1 ± 4.9	<0.001 ^a	<0.001 ^a	0.65
CI	1.0 ± 2.3	2.7 ± 1.8	2.4 ± 1.6	<0.001 ^a	0.002 ^a	0.58

Plus-minus values are means ± sd.

TEG[®] = thrombelastograph, preop = preoperative, intraop = intraoperative, postop = postoperative, R = reaction time to clot formation, K = coagulation time, MA = maximum amplitude of clot strength, α angle = angle of divergence, CI = coagulation index.

^aStatistically significant.

Hypercoagulability occurs during and immediately after surgical procedures (9,14). Possible causes of this coagulopathic state include dehydration, trauma, malignancy (15), sepsis, blood transfusions (16), hemodilution (17), and even anxiety (18). Activation of the hemostatic system may also be part of the body's normal response to surgical insult aimed at preventing excessive bleeding. Intracranial surgery, specifically, is associated with an increased incidence of coagulation disorders compared with general surgical procedures (4-7). The mechanism for this may be attributable to the release of tissue thromboplastin by injured brain and activation of the coagulation cascade (6). It is speculated that this phenomenon is more common in brain tumor patients because brain tumor cells have a higher thromboplastic activity, which may be a contributing factor (19,20). In addition, the amount of thromboplastin released is theoretically related to the extent of brain resection or tissue injury. Therefore, it has been speculated that with larger amounts of brain resected, more thromboplastin is released, leading to greater coagulopathy.

TEG[®] coagulation analysis provides a method for evaluation of the coagulation system from initial clot formation to clot retraction or dissolution. The tracing produced by TEG[®] analysis (Fig. 1) reveals information about the rapidity of clot formation, the strength of the formed clot, the presence of fibrinolysis (21), and platelet dysfunction (22). In addition, coagulation factor deficiencies, which may not be evident in terms

of abnormal PT and aPTT values until they are more than 50% reduced, may be reflected by abnormal TEG[®] indices. TEG[®] analysis is very sensitive in the identification and measurement of hypercoagulability, which is not detected by routine laboratory tests (8,9). Hypercoagulability is difficult to detect on standard coagulation tests unless the platelet count or fibrinogen concentration is markedly increased (23). TEG[®] variables indicative of hypercoagulability are a shortening of the R and K times, and an increase in MA and α angle. The TEG[®] CI is a description of the patient's overall coagulation and is derived from the R, K, MA, and α angle (see Appendix for formula). The normal range is between -2.0 and 2.0, which is equivalent to 2 standard deviations about the mean of zero. Outside this range, a positive CI indicates a hypercoagulable state; a negative CI indicates hypocoagulability. The test is simple to perform and has the advantage of providing information quickly to the anesthesiologist because the machine can be located in the operating room.

Although we did observe a hypercoagulable state postoperatively in these patients, no patient in this study developed a clinical coagulopathy, including clinically significant DVT or PE. However, we did not specifically screen for asymptomatic abnormalities such as using Doppler or ultrasound to examine leg veins. Therefore, no conclusions can be drawn regarding the relationship between TEG[®] variables and thrombotic complications in this study.

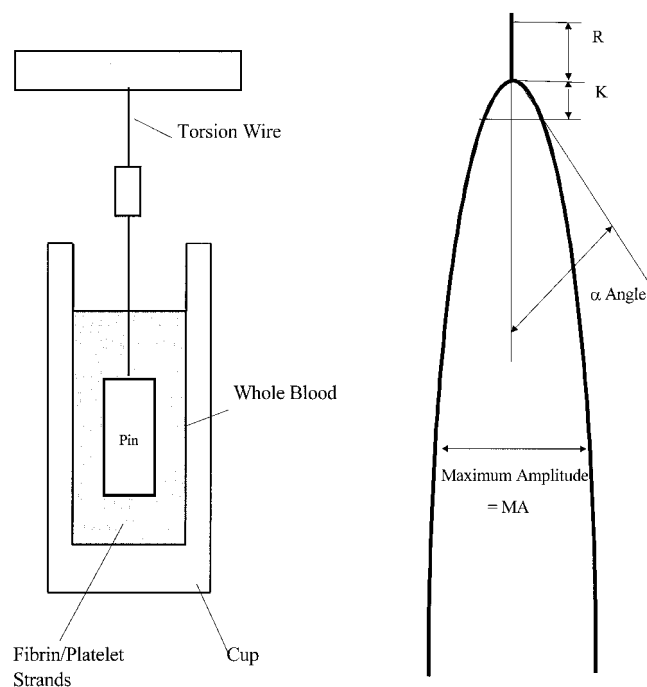


Figure 1. Diagram of thrombelastograph[®] instrument and the tracing it produces. The instrument diagram shows the sample cup and measurement pin, which is attached to a calibrated torsion wire. Blood is placed in the cup and allowed to clot as the cup oscillates. The elastic shear modulus of the sample is measured as fibers composed of fibrin and platelets are formed and attach to the cup and pin. The width or the tracing produced is proportional to the elastic shear modulus; it is larger with a hypercoagulable state. Refer to the text for a description of the tracing measurements. R = reaction time to clot formation, K = coagulation time.

Hypercoagulability in the perioperative period was observed for both native and celite sampling techniques, reaching significance with the celite technique only. As an adjunct to native whole blood, celite accelerates whole blood coagulation by activating coagulation factors and platelets. Celite consists of chemically inert particles (silica) that provide a contact surface to activate factor XII and platelets and, hence, accelerate coagulation in a blood sample (23). It is thought that the activation of coagulation for TEG[®] analysis is useful both to shorten and reduce variability in onset time and to permit earlier assessment of clot strength and integrity (24,25). We used both native and celite techniques to ascertain whether a difference could be detected between the two methods. This was indeed the case. In our study, celite samples showed significant results whereas native samples trended in the same direction but did not reach significance. Perhaps this is attributable to the fact that there was more inherent variability in the native sampling technique, which was reduced by using the celite technique. This study suggests that the native technique is inadequate for perioperative assessment of hypercoagulability in this setting.

In conclusion, TEG[®] data can be used to assess coagulation perioperatively and to demonstrate that hypercoagulability develops early after brain resection in pediatric patients. The use of TEG[®] data to monitor pediatric neurosurgical patients may help to identify those at increased risk postoperatively for thromboembolic events. Further investigations are needed to determine the clinical significance of this hypercoagulable state and the mechanism responsible for its development.

Appendix

TEG[®] Coagulation Index Calculation

Native whole blood:

$$CI = -.1227R + .0092K + .1665MA - .0241\alpha - 5.0220$$

Celite-activated whole blood:

$$CI = -.3258R - .1886K + .1224MA + .0759\alpha - 7.7922$$

TEG[®] = thrombelastograph, CI = coagulation index, R = reaction time to clot formation, K = coagulation time, MA = maximum amplitude of clot strength, alpha angle = angle of divergence.

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