BASIC INVESTIGATIONS

Utility of an Initial D-dimer Assay in Screening for Traumatic or Spontaneous Intracranial Hemorrhage

MARK E. HOFFMANN, MD, O. JOHN MA, MD, GARY GADDIS, PHD, MD

Abstract. **Objective:** To evaluate the sensitivity of a D-dimer assay as a screening tool for possible traumatic or spontaneous intracranial hemorrhage. If adequately sensitive, the D-dimer assay may potentially permit omission of a more expensive computed tomography (CT) scan of the head when such hemorrhage is clinically suspected. **Methods:** Prospective, consecutive, blinded study of patients (age > 16 years) requiring a CT scan of the head for suspected intracranial hemorrhage over a five-month period at a university, Level I trauma center. All study patients had a serum D-dimer assay obtained prior to their CT scans. Sensitivity and specificity, with 95% confidence intervals (95% CIs), of the enzyme-linked immunosorbent assay (ELISA) D-dimer assay for the detection of intracranial hemorrhage were calculated. **Results:** Of the 319 patients entered in the study, 25 (7.8%) had a CT scan positive for intracranial hemorrhage. Patients with intracranial hemorrhage were more likely to have a positive D-dimer assay (chi-square = 13.075, $p < 0.001$). The D-dimer assay had 21 true-positive and four false-negative tests, resulting in a sensitivity of 84.0% (95% CI = 63.7% to 95.5%) and a specificity of 55.8% (95% CI = 55.5% to 55.9%). The four false-negative cases included one small intraparenchymal hemorrhage, one small subarachnoid hemorrhage, one moderate-sized intraparenchymal hemorrhage with mid-line shift, and one large subdural hematoma requiring emergent surgery. **Conclusions:** Due to the catastrophic nature of missing an intracranial hemorrhage in the emergency department, the D-dimer assay is not adequately sensitive or predictive to use as a screening tool to allow routine omission of head CT scanning. **Key words:** D-dimer assay; intracranial hemorrhage; computed tomography; head injury. ACADEMIC EMERGENCY MEDICINE 2001; 8:859–865

HEAD INJURY with intracranial hemorrhage is a factor in 50% of all trauma-related fatalities and 75% of motor vehicle crash fatalities.[1] Up to 20% of all cerebral vascular accidents are hemorrhagic.[2] Suspected intracranial hemorrhage is a common reason for emergency physicians (EPs) to obtain a computed tomography (CT) scan of the head since it is medically unacceptable to fail to diagnose these conditions. Radiation dosage, patient throughput time in the emergency department (ED), utilization of radiologic technicians, and financial and other costs accrue from liberal use of CT scanning. However, physician and patient expectations, as well as medicolegal concerns, dictate that EPs actively screen for intracranial hemorrhage. If an effective, sensitive, reliable, and less costly screening test for intracranial hemorrhage could be identified, the number of CT scans of the head that are negative for intracranial hemorrhage might be reduced.

A D-dimer assay represents a theoretically attractive candidate for such a screening test. The brain contains high concentrations of tissue factors that, if released into the circulation due to disruption of the blood–brain barrier, trigger the activation of the extrinsic coagulation pathway.[3,4] An accepted hypothesis states that the magnitude of intravascular coagulation is proportional to the amount of brain tissue disrupted following brain injury.[3,5–9] The prognosis for severe head injury has been based on the results of CT scanning, assays for coagulopathy, and the neurological examination. More recent studies have demonstrated the D-dimer assay and other serum markers of coagulopathy to be sensitive and reliable indicators for head injury prognosis.[10–12] Enzyme-linked immunosorbent assay (ELISA) assays are known to be highly sensitive for the presence of D-dimer.[13] Our laboratory can complete D-dimer assays within 30 minutes of receipt of the sample.

From the Department of Emergency Medicine, Truman Medical Center (MEH, OJM), and the Department of Emergency Medicine, St. Luke's Hospital (GG), University of Missouri–Kansas City School of Medicine, Kansas City, MO.
Received February 15, 2001; revision received May 16, 2001; accepted May 21, 2001. Presented at the SAEM annual meeting, San Francisco, CA, May 2000.
Address for correspondence and reprints: Mark E. Hoffmann, MD, 7092 SE 43rd Avenue, St. Cloud, MN 56304. e-mail: crazydiamond@aol.com

TABLE 1. Inclusion Criteria

Injury or symptom onset < 24 hours
Loss of consciousness
Suspected skull fracture
Glasgow Coma Scale score < 13
Focal neurological deficit
Age > 60 years with mental status changes
Suspected subarachnoid hemorrhage
New or post-traumatic seizure
Worsening mental status

TABLE 2. Exclusion Criteria

Age < 16 years
Injury or symptoms > 24 hours
Known pre-existing deep venous thrombosis, pulmonary embolism, cancer, or cirrhosis
Major surgery < 2 weeks
Penetrating eye injury
Pregnancy
Multisystem trauma to chest, abdomen, or extremities

Although an association between brain injury and coagulopathy has been known for two decades, to the best of our knowledge, no study has evaluated the sensitivity of the D-dimer assay as a potential screening tool for patients with suspected intracranial hemorrhage. We hypothesized the D-dimer assay would have a sufficiently high sensitivity and negative predictive value for intracranial hemorrhage to permit the D-dimer assay to serve as an effective screen for intracranial hemorrhage. This implies that to safely reduce the number of CT scans of the head, the sensitivity and negative predictive value of a D-dimer assay for intracranial hemorrhage must approach 100%. The objective of this study was to prospectively assess whether an initial D-dimer assay can safely screen patients for clinically suspected traumatic or spontaneous intracranial hemorrhage by achieving a sensitivity and negative predictive value of 100%.

METHODS

Study Design. This was a prospective clinical observational study of patients suspected to have intracranial hemorrhage. The study was approved by the institution's investigational review board.

Study Setting and Population. This prospective study consecutively enrolled adult patients (age ≥ 16 years) between June 1, 1999, and November 30, 1999. Specific inclusion and exclusion criteria are detailed in Tables 1 and 2. Age of suspected intracranial hemorrhage, based on history, was stratified as 0–3 hours, 3–12 hours, or 12–24 hours. Intracranial hemorrhage suspicion was based on the clinical opinion of the attending staff or third-year emergency medicine resident, derived from history, physical examination, and other available data. The setting was an ED of a university Level I trauma center, with an annual volume of 53,000 patients.

Study Protocol. Upon decision to screen for intracranial hemorrhage by CT scan of the head, blood was obtained from intravenous line placement, then sent in a 3.2% sodium citrate ("blue top") test tube to our hospital's laboratory for prompt centrifugation and cooling to negative 20°C. The D-dimer assay kits, donated by Instrumentation Laboratory Company (Lexington, MA), were an automated latex-enhanced immunoassay for the quantitative determination of D-dimer in human citrated plasma. D-dimer assay results were reported in ng/mL; the upper limit of normal as stated by our laboratory and the package insert was 284 ng/mL and 278 ng/mL, respectively. D-dimer assays were performed biweekly, with results recorded on data sheets separate from CT results. This ensured that both investigators and clinicians were blinded to the results. The assay package insert states that for up to eight weeks, the D-dimer assay remains accurate when cooled to a temperature of −20°C.

All CT scans were initially interpreted by EPs and radiology residents, and then formally overread by staff radiologists within 24 hours. Patients with intracranial hemorrhage were admitted to either the neurosurgery or the internal medicine service.

A single investigator reviewed patient medical records twice weekly in order to assess accuracy of enrollment, CT scan results, patient disposition, and collection of relevant data. The data collection sheets recorded patient age and gender, indications for CT scan, time since injury (0–3 hours, 3–12 hours, or 12–24 hours), time blood was drawn, and associated illness or injury.

Data Analysis. Sample size estimation was done. The critical point of this study, however, is the sensitivity of the D-dimer assay, not the presence of a sample size adequate to find a significant difference between populations with and without a positive D-dimer assay.

Nonetheless, we knew from a retrospective review at our institution that of 1,110 patients with a CT scan obtained to screen for intracranial hemorrhage, 46 scans were positive for intracranial hemorrhage. Of these 46, 42 were known to have a positive D-dimer assay. D-dimer assays for the other four patients were unavailable. Also, the prevalence of positive and negative D-dimer assays among patients with CT scans negative for intracranial hemorrhage was unknown. These facts

precluded use of a retrospective survey to assess D-dimer assay as a screen for intracranial hemorrhage. Some false-positive cases (positive D-dimer assay with negative intracranial hemorrhage) would be expected in this series due to the presence of concomitant injuries. We utilized a projected 50% rate for patients with CT scans negative for intracranial hemorrhage having elevated D-dimer levels to estimate required sample size. Although this rate was higher than expected, it was chosen to ensure adequate power.[14] With these assumptions, a sample size of 266 patients or more would achieve a power of at least 0.8.

Chi-square testing was done to evaluate for any significant difference of proportion of positive D-dimer levels between patients whose CT scans were positive and negative. Sensitivity, specificity, negative predictive value, and positive predictive value, along with their 95% confidence intervals (95% CIs), were calculated. Because the "cutoff" point for a "positive" test is somewhat arbitrary, receiver operating characteristic (ROC) curves were constructed for D-dimer results.

The most critical aspect of D-dimer assay testing, in keeping with the objective and our hypothesis, was the sensitivity of a positive D-dimer assay for the presence of intracranial hemorrhage. If the 95% CI of D-dimer sensitivity did not include 100%, then D-dimer assay testing would clearly fail to serve as an adequate screening test for intracranial hemorrhage.

RESULTS

Overall, 455 patients were identified as meeting criteria for inclusion in the study; 319 patients were enrolled. Table 3 notes the characteristics of the enrolled patients.

Twenty-five (7.8%) of the 319 study patients had intracranial hemorrhage identified on CT scan (Table 4). Of these 25 patients with intracranial hemorrhage, 21 had positive D-dimer assays (true positives) and four had normal assays (false negatives). The calculated test sensitivity was 84% and the confidence interval for sensitivity did not overlap 100%.

TABLE 3. Characteristics of the Subjects

Gender	
Male	204/319
Female	115/319
Age	41.14 ± 17.4 (16–99)
Type of injury	
Nontrauma	131/319
Trauma	188/319
Mechanisms of traumatic injuries (in descending order of prevalence)	
Motor vehicle crash	
Blunt object to head	
Fall from a height	

Continuous variables expressed as mean ± SD (range). Categorical variables expressed as proportions.

TABLE 4. Types of Intracranial Hemorrhage on Computed Tomography Scan of the Head

Subdural hematoma	7
Subarachnoid hemorrhage	7
Intraparenchymal hemorrhage	6
Intracerebral contusion	5

TABLE 5. Sensitivity, Specificity, Positive Predictive Value, and Negative Predictive Value for the Initial D-dimer Assay in Screening for Intracranial Hemorrhage

	CT Positive	CT Negative	Total
Positive D-dimer assay	21	130	151
Negative D-dimer assay	4	164	168
TOTAL	25	294	319

CT = computed tomography. Sensitivity: 84.0% (95% CI = 63.7% to 95.5%); specificity: 55.8% (95% CI = 50.1% to 61.5%); positive predictive value: 13.9% (95% CI = 8.8% to 19.7%); negative predictive value: 97.6% (95% CI = 94.1% to 99.3%).

Table 5 demonstrates the sensitivity, specificity, negative predictive value, and positive predictive value for the D-dimer assay in screening for intracranial hemorrhage. Patients with intracranial hemorrhage were more likely to have elevated D-dimer levels (chi-square = 13.075, df = 1, $p < 0.001$).

Figure 1 demonstrates a ROC curve for the D-dimer assay, in recognition that our laboratory's "cutoff" value for "normal" is somewhat arbitrary. A "cutoff" of 131 ng/mL would have permitted a 100% sensitivity, but would have markedly increased the number of false-positive test results. The failure of the ROC curve to approach the upper left corner of the graph shows that alternative "cutoff" values for a positive test would not permit D-dimer assay to be highly predictive of hemorrhage.

The time interval between injury and obtaining blood from the four false-negative patients ranged between three hours and 24 hours. The four false-negative patients had the following outcomes: patient 1 was a 26-year-old woman who had a spontaneous, atraumatic intracerebral hemorrhage that required no surgical intervention. During the patient's hospitalization, the D-dimer assay was initially 131 ng/mL and remained negative (161 ng/mL) on repeat testing 12 hours after presentation. Patient 2 was a 19-year-old man who complained of a headache and loss of consciousness after a fall and presented within three hours

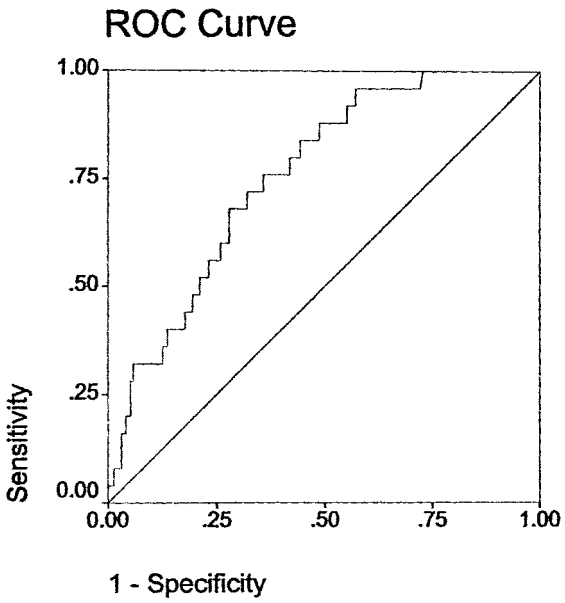
ROC Curve

Case Processing Summary

CT_QUAL	Valid N (listwise)
Positive[a]	25
Negative	294

Larger values of the test result variable(s) indicate stronger evidence for a positive actual state.

a. The positive actual state is 2.



Diagonal segments are produced by ties.

Area Under the Curve

Test Result Variable(s): D-d Quant

Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
			Lower Bound	Upper Bound
.759	.043	.000	.675	.842

The test result variable(s): D-d Quant has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

Figure 1. Receiver operating characteristic (ROC) curve for D-dimer assay data as a predictor of the presence or absence of intracranial hemorrhage. CT = computed tomography.

of symptom onset. He was diagnosed as having a small subarachnoid hemorrhage. The patient required no surgical intervention. The initial D-dimer level was 210 ng/mL. This patient was discharged home without a repeat D-dimer assay having been obtained during the hospital course. Patient 3 was a 40-year-old man who presented less than three hours after developing altered mental status and was diagnosed as having a spontaneous, atraumatic, moderate-sized intraparenchymal hemorrhage with mid-line shift. The initially normal D-dimer level of 258 ng/mL turned positive (416 ng/mL) on repeat testing 12 hours after initial presentation. This patient had a right hemiparesis and was discharged to a long-term care facility for rehabilitation. Patient 4 was a 41-year-old man who fell, experienced a seizure, and presented less than three hours after symptom onset. He was diagnosed as having a large subdural hematoma that necessitated an emergent craniotomy. The initial D-dimer level was 227 ng/mL. This patient had a positive D-dimer assay (788 ng/mL) drawn the morning following emergency craniotomy. The patient was discharged five days postoperatively without any neurological sequelae.

DISCUSSION

In this study, the sensitivity of the D-dimer assay as a screen for suspected intracranial hemorrhage was 84% (95% CI = 63.7% to 95.5%). This sensitivity is inadequate for us to advocate the use of a D-dimer assay as a screening tool for intracranial hemorrhage even though the patients with intracranial hemorrhage were statistically more likely to have an elevated D-dimer level.

The D-dimer, a fragment of degradation products of cross-linked fibrin, is direct evidence of fibrin formation and its dissolution by plasmin. Currently, the D-dimer assay is the most sensitive test for identifying this process.[12] ELISA kits of various manufacturers are known to be more sensitive than semiquantitative latex agglutination studies.[13] Assay systems for D-dimer antigen include manual immunoagglutination assays, immunofiltration assays, microtiter plate ELISA assays, automated ELISA systems, and latex-enhanced photometric immunoassays. There are at least 13 different assays commercially available. According to clinical studies, the characteristics of the different reagents and methods that are used in various laboratories yield a large variation in sensitivities.[15]

Previous studies have evaluated fibrinolytic parameters in the prognosis of head injury.[9–11] A strong association between coagulopathy at admission and poor neurological outcome was confirmed by data obtained from the National Traumatic Coma Data Bank. One study concluded that the fibrinolytic parameters found on admission could be reliable indicators of head injury outcome. When the D-dimer assay was elevated two- to three-fold, 92% of patients died regardless of the level of consciousness at admission.[16] These patients were evaluated within two hours of their injuries; no data were available for evaluating the D-dimer assay as a screening tool for intracranial hemorrhage.

It is possible that the D-dimer assay failed to adequately screen intracranial hemorrhage in our study because inadequate time may have elapsed between hemorrhage and the crossing of the damaged blood–brain barrier by fibrin degradation products into the circulation. Three of the four patients with false-negative results in our study presented within three hours after symptom onset or injury. Currently, to the best of our knowledge, there are no studies that investigate the time of duration required from initial brain injury to the time when the presence of fibrin degradation products in the systemic circulation can be adequately measured. Another possibility is that not all patients with intracranial hemorrhage and disruption of the blood–brain barrier develop coagulopathy.

Some investigators have compared the coagulopathies between patients with isolated head injury and trauma patients without head injury. Nanzaki and Kemmotsu reported the coagulofibrinolytic changes after isolated head injury were not different from those in trauma patients without head injury. This was a small study consisting of five patients with isolated head injury and 11 trauma patients without head injury.[17] Another study found the D-dimer assay to be overly sensitive in predicting head injury outcome in trauma patients. This study also compared the coagulopathies between trauma patients and elective neurosurgical patients. The D-dimer levels of the neurosurgical patients were normal or near normal. The authors proposed an additional factor, such as catecholamine release, might be involved in trauma-related brain injury by amplifying the process of disseminated intravascular coagulopathy.[8]

Recent studies in head injury have evaluated the protein S-100. This protein is contained within the astroglial cells of the central nervous system. Injury to these cells releases S-100 into the circulation and can be quantified serologically. Most studies have found this protein to be a reliable indicator of head injury prognosis.[18–23] One of the studies found the S-100 protein had a potential role as a screening test. The investigators calculated the negative predictive value of the S-100 protein to be 99% and an undetectable serum S-100 level predicted normal intracranial findings on CT scan. They concluded the S-100 marker might be used to select patients for CT scanning.[24] The S-100 serum marker, however, is unavailable in most hospital laboratories.

Increase in blood–brain barrier permeability after subarachnoid hemorrhage may be a time-dependent event. Few studies have examined the relationship between subarachnoid hemorrhage and blood–brain barrier permeability. There have been conflicting reports due to limitations in experimental probes adopted and in timing of observation. One study by Germano et al. found significant permeability changes beginning at 36 hours after subarachnoid hemorrhage[25]; a study by Trojanowski found extravasation and tissue staining only four hours after bleeding.[26] Johshita et al. suggested that barrier disturbances associated with subarachnoid hemorrhage may be multifactorial in time course and location.[27]

LIMITATIONS AND FUTURE QUESTIONS

There are several limitations to this study. First, specific, widely accepted criteria do not exist regarding which patient requires a CT scan of the head in the ED for evaluation of intracranial hemorrhage. Second, the D-dimer assay is not a stan-

dardized test between various facilities. We evaluated just one of several types of ELISA D-dimer assays. Various D-dimer assays, however, have similar sensitivities and specificities for coagulopathy when evaluating for deep venous thrombosis.[13] Third, 136 (30%) potential study patients were excluded due to inadequate data collection sheet completion by the clinician (18), misplaced D-dimer assay or inappropriately stored specimen by ancillary services (76), or hemolyzed specimen (42). Fourth, not all patients admitted with the diagnosis of intracranial hemorrhage had repeat D-dimer assays by the admitting services. Fifth, patients who were discharged from the ED with normal CT scans and false-positive D-dimer assays did not have sufficient follow-up with repeat CT scanning to fully assess for delayed injury. Sixth, the D-dimer assay was an ELISA assay that, though more sensitive than the semiquantitative latex agglutination tests, does take longer to perform than a latex agglutination study.[13] Finally, no validated criteria of which we are aware assess a pretest probability of intracranial hemorrhage in patients suspected to have intracranial hemorrhage. We did not attempt to create such criteria in this study. Patients were eligible for study entry if the patient's physician had clinical suspicion of an intracranial hemorrhage as noted by the inclusion criteria. The factors that led to the decision to perform CT scanning were not quantified.

Future studies should address the time-dependent issue of D-dimer assays with the onset of severe headache or traumatic event. Also, future investigations should prospectively review patient outcomes after head injury with the results of serial D-dimer assay testing. In addition, development of a scale utilizing history and physical examination data to assess pretest probability of hemorrhage would provide a focus for subsequent study.

CONCLUSIONS

Patients with intracranial hemorrhage are more likely than not to have an elevated D-dimer assay. Due to the catastrophic nature of missing an intracranial hemorrhage, however, the D-dimer assay is not adequately sensitive or predictive to use as a screening tool. The D-dimer assay cannot be relied upon as a substitute for an emergent CT scan of the head when intracranial hemorrhage is clinically suspected.

The authors thank Jamie Patel, MD, for her assistance during the data collection phase of this study. They also thank Instrumentation Laboratory Company (Lexington, MA) for donating the D-dimer assay kits at no expense to the patient.

References

1. Kalsbeek WD, McLaurin RL, Harris BS III, et al. The National Head and Spinal Cord Injury Survey: major findings. J Neurosurg. 1980; 53:19–31.
2. Brott TG, Thalinger K, Hertzberg V. Hypertension as a risk for spontaneous intracerebral hemorrhage. Stroke. 1986; 17: 78–83.
3. Hulka F, Mullins R, Frank E. Blunt brain injury activates the coagulation process. Arch Surg. 1996; 131:923–8.
4. Bredbacka S, Edner G. Soluble fibrin and D-dimer as detectors of hypercoagulability in patients with isolated brain trauma. J Neurosurg Anesthesiol. 1994; 6(2):75–82.
5. Scherer RU, Spangenberg P. Procoagulant activity in patients with isolated severe head trauma. Crit Care Med. 1998; 26(1):149–56.
6. Becker S, Schneider W, Kreuz W, Jacobi G, Scharrer I, Nowak-Gottl U. Post-trauma coagulation and fibrinolysis in children suffering from severe cerebro-cranial trauma. Eur J Pediatr. 1999; (158 suppl 3):S197–S202.
7. Olson JD, Kaufman HH, Moake J, et al. The incidence and significance of hemostatic abnormalities in patients with head injuries. Neurosurgery. 1989; 24:825–32.
8. Kearney TJ, Bentt L, Grode M, Lee S, Hiatt JR, Shabot MM. Coagulopathy and catecholamines in severe head injury. J Trauma. 1992; 32:608–12.
9. Stein SC, Young GS, Talucci RC, Greenbaum BH, Ross SE. Delayed brain injury after head trauma: significance of coagulopathy. Neurosurgery. 1992; 30:160–5.
10. Raabe A, Grolms C, Keller M, Dohnert J, Sorge O, Seifert V. Correlation of CT findings and serum brain damage markers following severe head injury. Acta Neurochir. 1998; 140: 787–91.
11. Woertgen C, Rothoerl RD, Metz C, Brawanski A. Comparison of clinical, radiologic, and serum marker as prognostic factors after severe head injury. J Trauma. 1999; 47:1126–30.
12. Bick RL, Baker WF. Diagnostic efficacy of the D-dimer assay in disseminated intra-vascular coagulation (DIC). Thromb Res. 1992; 15:785–90.
13. van der Graaf F, van den Borne H, van der Kolk M, et al. Exclusion of deep venous thrombosis with D-dimer testing: comparison of 13 D-dimer methods in 99 outpatients suspected of deep venous thrombosis using venography as a reference standard. Thromb Haemost. 2000; 83:191–8.
14. Glantz SA. Primer of Biostatistics: The Program. New York: McGraw-Hill, 1992.
15. DeMaat MP, Meijer P, Nieuwenhuizen W, et al. Performance of semiquantitative and quantitative D-dimer assays in the ECAT external quality assessment program. Semin Thromb Hemost. 2000; 26:625–30.
16. Takahashi H, Urano T, Takada Y, Nagai N, Takada A. Fibrinolytic parameters as an admission prognostic marker of head injury in patients who talk and deteriorate. J Neurosurg. 1997; 86:768–72.
17. Nanzaki S, Kemmotsu O. Coagulofibrinolytic changes after isolated head injury are not different from those in trauma patients without head injury. J Trauma. 1999; 46:1070–6.
18. Rothoerl RD, Woertgen C, Holzachuh M, Metz C, Brawanski A. S-100 serum levels after minor and major head injury. J Trauma. 1998; 45:765–7.
19. Raabe A, Grolms C, Seifert V. Serum markers of brain damage and outcome prediction in patients after severe head injury. Br J Neurosurg. 1999; 13(1):56–9.
20. Ingebrigtsen T, Waterloo K, Jacobsen EA, Lanbakk B, Romner B. Traumatic brain damage in minor head injury: relation of serum S-100 protein measurements to MRI and neurobehavioral outcome. Neurosurgery. 1999; 45:468–76.
21. Raabe A, Grolms C, Sorge O, Zimmermann M, Seifert V. Serum S-100B protein in severe head injury. Neurosurgery. 1999; 45:477–83.
22. Woertgen C, Rothoerl RD, Metz C, Brawanski A. Comparison of clinical, radiologic, and serum marker as prognostic factors after severe head injury. J Trauma. 1999; 47:1126–30.
23. Hermann M, Jost S, Kutz S, et al. Temporal profile of release of neurobiochemical markers of brain damage after traumatic brain injury is associated with intracranial pathology as

demonstrated in cranial computerized tomography. J Neurotrauma. 2000; 17:113–22.
24. Romner B, Ingesbrigtsen T, Kongstad P, Borgesen SE. Traumatic brain damage: S-100 protein measurements related to neuroradiological findings. J Neurotrauma. 2000; 17:641–7.
25. Germano A, d'Avella D, Imperatore C, et al. Time-course of blood brain barrier permeability changes after experimental subarachnoid hemorrhage. Acta Neurochir. 2000; 142:575–80.
26. Trojanowski T. Blood–brain barrier changes after experimental subarachnoid hemorrhage. Acta Neurochir. 1982; 60: 45–54.
27. Johshita H, Kassell NF, Sasaki T, et al. Blood–brain barrier disturbance following subarachnoid hemorrhage in rabbits. Stroke. 1990; 21:1051–8.