Prognostic Value of Admission Laboratory Parameters in Traumatic Brain Injury: Results from the IMPACT Study

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ABSTRACT

Abnormalities in laboratory parameters are frequent following traumatic brain injury (TBI), but few studies have investigated their predictive value. We aimed to describe and quantify the relation between laboratory parameters that are routinely determined on admission and final outcome following TBI. Individual patient data were available in the IMPACT database from six Phase III randomized controlled trials and one observational study in TBI. We studied glucose (N = 4834), sodium (N = 3398), hemoglobin (Hb, N = 3875), platelet count (N = 1629), and prothrombin time (PT; N = 840) for their associations with outcome at 6 months (Glasgow Outcome Scale [GOS]). We used logistic regression models with linear, quadratic, and restricted cubic spline functions. The strength of the associations was expressed as an unadjusted odds ratio, calculated over the shift in outcome between the 25th and 75th percentiles. Proportional odds methodology was further applied to quantify the strength of the associations across the full range of the GOS. All parameters were consistently associated with outcome in a continuous relationship: glucose and prothrombin time showed a positive linear relation to outcome (i.e., increasing values associated with poorer outcome) and Hb, platelets, and pH an inverse linear relation (i.e., low values associated with poorer outcome). Sodium demonstrated a U-shaped relation to outcome, with low levels being more strongly related to poorer outcome. Effects were strongest for increasing levels of glucose (odds ratio 1.7; 95% CI 1.54–1.83) and decreasing levels of Hb (odds ratio 0.7; CI 0.60–0.78). Higher glucose values were associated with increasing age, but on adjusted analysis, the strength of the association with outcome remained. Whether treatment of abnormal values may improve outcome needs further rigorous study.

Key words: glucose; hemoglobin; laboratory parameters; outcome; prognosis; sodium; traumatic brain injury
INTRODUCTION

Many studies have reported the prognostic value of clinical and radiological parameters in traumatic brain injury (TBI), but relatively few have investigated the relation between laboratory parameters on admission and final outcome. A number of studies suggest prognostic significance of coagulation parameters, hemoglobin (Hb), and glucose in TBI. Low platelet counts are related to progressive hemorrhage after TBI (Engstrom et al., 2005), and small studies have shown a relation between decreased platelet counts and poorer outcome in children (Chiaretti et al., 2001) and adults (Lannoo et al., 2000). This relation was not observed in other studies, and assessment of platelet function is considered more relevant than the actual platelet count (Jacoby et al., 2001). Decreased Hb has also been shown to be associated with poorer outcome (Sanchez-Olmedo et al., 2005). The presence of hypotension is an important systemic secondary insult (Miller et al., 1978) and strongly related to poorer outcome (Chesnut et al., 1993; Schreiber et al., 2002; Manley et al., 2001), although the relative prognostic value of decreased Hb and platelet levels in relation to hypotension or to the actual levels of systolic blood pressure has not been reported. The strongest evidence of the prognostic value of admission laboratory parameters exists for glucose, higher levels being related to poorer outcome (Young et al., 1989; Lannoo et al., 2000; Walia and Sutcliffe, 2002; Rovlias and Kotsou, 2000). Critical threshold values have been proposed (Lam et al., 1991; Yang et al., 1995; Rovlias and Kotsou, 2000, 2004), but whether these indeed exist, or whether the relation between increased glucose levels and poorer outcome is in fact continuous has never been studied.

Abnormalities in some laboratory parameters may mainly be an expression of the degree of injury (Margulies et al., 1994), but for other parameters, abnormalities may induce further damage or delay the recovery process. For example, hyponatremia may aggravate cerebral edema and coagulopathy may accelerate bleeding of contusions. Hyperglycemia may also aggravate pathophysiological pathways (Zou et al., 2002) and cause a further disruption of the microcirculation, which is already compromised in TBI.

Analyses of the prognostic value of laboratory parameters in TBI are particularly relevant as these are routinely measured and objective. Most importantly, abnormal values can be corrected by treatment, in contrast to demographics such as age or radiological parameters, which mainly reflect the severity of injury (e.g., Glasgow Coma Scale [GCS], computerized tomography [CT] scan). The IMPACT database on TBI patients (Marmarou et al., 2007) permitted us to perform a robust analysis of the prognostic value in TBI of laboratory parameters that are routinely assessed on admission.

METHODS

Patients and Data Collection

Within the IMPACT database (Marmarou et al., 2007) values of laboratory parameters on admission were available from six randomized controlled trials (RCTs) on neuroprotective agents (Tirilazad trials [TINT, TIUS] (Marshall et al., 1998, Hukkelhoven et al., 2002), Saphir study (SAP), PEGSOD study (PEG), (Young et al., 1989), HIT I nimodipine study (HIT I) (Bailey et al., 1991), the Bradycor trial (SKB) (Marmarou et al., 1999), and one observational study (Traumatic Coma Databank [TCDB]) (Foulkes et al., 1991). These studies contained different sets of laboratory parameters, and the number of patients varied per variable. We considered laboratory parameters that (a) were available in most datasets, (b) which could be linked to pathophysiologic cascades causing secondary damage, or (c) of which prognostic value had been reported in previous studies. The following laboratory variables were included in our analyses: glucose (N = 4834; mmol/L), sodium (N = 5270; mmol/L), pH (N = 3398), hemoglobin (Hb; N = 3875; g/dL), platelet count (N = 1629; 10^9/L), and prothrombin time (PT; N = 840; sec). Units of measurement were converted to SI units where necessary. The primary endpoint for prognostic analysis was the Glasgow Outcome Scale (GOS) as recorded in the studies. If the 6-month GOS was missing, we imputed the 3-month GOS (N = 1613, including 1510 patients from the PEGSOD trial).

Data Analysis

In the prognostic analysis of continuous variables, results can be substantially influenced by the presence of outliers. The robustness of our statistical analysis was increased in two ways: First, we examined distributions of laboratory values to identify biologically impossible values. Second, we applied a truncation procedure to limit the influence of extreme values. Truncation procedures shift values from outside pre-specified ranges towards the endpoint of the range (truncation points). Box plots and histograms were used to detect outliers and define the truncation points. These analyses were performed separately for each study as well as for all studies combined. Three patients had measurements of a glucose level above 100 mmol/L, and these were set to missing. The lower and upper truncation points for each laboratory variable...
were set as follows: for glucose, 3–20 mmol/L; for sodium, 125–155 mmol/L; for hemoglobin, 6–17 g/dL; for hematocrit, 18–50%; for pH, 7.0–7.7; for platelets, 0–450 x 10^9/L; and for prothrombin time, 0–20 sec.

The number of truncated values was less than 1% for each laboratory variable.

In some studies, Hb values were missing, but hematocrit (Ht) values present. In these cases, missing Hb values (N = 505) were imputed from Ht based on a linear regression model that included Ht and gender. This model had an adjusted R^2 of 0.97.

**Statistical Analysis**

Median and interquartile ranges were calculated for descriptive purposes. We also determined the prevalence of abnormal values, as defined by WHO common toxicity criteria for grading of adverse events.

The relationship between laboratory variables and outcome was first analyzed by crosstabulation. The shape of the relationship of each laboratory parameter to six month outcome was further examined in univariate analysis with linear, linear and quadratic and restricted spline functions. These functions are smooth but flexible, and allow for an adequate description of non-linear relationships. We also searched for change points in the relationships by adding a linear term that was truncated at the considered change point and studying the increase in Nagelkerke’s R^2 as measure of predictive performance.

Logistic regression models were applied to quantify the predictive strength of the laboratory parameters considered. In these regression models the GOS was dichotomized in four different ways: less than good recovery versus good recovery, unfavorable outcome versus favorable outcome, death/vegetative versus conscious survival, and death versus survival. We also considered an ordinal analysis with proportional odds methodology, which reflects prognostic effects across the various GOS categories (McHugh et al., 2007). Finally multivariate analysis was performed, adjusting for the main clinical predictors: age, motor score and pupils.

The strength of the associations was expressed as an odds ratio with 95% confidence intervals. In order to obtain comparable odds ratios for the linear relationships we rescaled each variable in the following way: the original values were divided by the difference between the 75 and 25 percentile values (p75–p25). Hence the odds ratios refer to the effect of a shift in values from the lower to the upper end of the interquartile range of each variable. For sodium, which had a U-shaped relation with GOS, we created three categories: low (<p25), intermediate (p25–p75) and high (>p75) level of sodium. We calculated the odds ratios with the intermediate group as the reference category.

**RESULTS**

**Distributions and Descriptive Analysis**

The availability of laboratory data within the datasets and the respective median values are summarized in Table 1. Sodium values (N = 5270) were most complete, being available for each of the seven studies. Glucose (N = 4834) and Hb (N = 3875) were available in the majority of patients from six studies, and pH in 3398 patients from five studies. Data on platelets and prothrombin time were more limited and only available in four and three datasets respectively. The lower numbers are mainly caused by the absence of a laboratory parameter in some of the datasets rather than by missing values within datasets. The percentage of patients with laboratory values recorded was considerably lower in the observational study (TCDB) than in the RCTs. The relatively low percentage of data available in the PEGSOD dataset reflects that this dataset contained results from separate substudies.

The median values of recorded platelet counts were slightly higher in the PEGSOD and TCDB studies and prothrombin time longer in the relatively small Bradycor trial (SKB). Abnormal values were noted most frequently for glucose (83%). The values for pH were often lower (34%) or higher (25%) than WHO ranges (7.35–7.45) and prothrombin time was prolonged in 26% of cases (Table 2). The recorded values for sodium, platelets and Hb were generally within normal ranges.

**Laboratory Values and Outcome**

All laboratory parameters studied were significantly related to outcome. A positive linear relation was observed for glucose and prothrombin time, higher values being associated with poorer prognosis and a negative linear relation for pH, platelets and Hb. Figure 1 illustrates that this relationship is continuous without any clear indication for the presence of threshold values. No change points were identified that led to a better predictive performance, despite the impression that effects flatten for glucose levels below 6 mmol/L, for pH > 7.45, for platelets > 200, and for Hb > 15 g/dL. Both low and high levels of sodium were related to poorer outcome (Fig. 1).

Figure 2 shows the median laboratory values and percentile ranges within grouped GOS categories. In those with poorest outcome (death/vegetative), glucose was higher, sodium levels lower, PT longer and Hb lower. Logistic regression analysis showed the most substantial prognostic effects for glucose (OR 1.7) and for hemoglobin (OR 0.69; Table 3). These effects were somewhat
### TABLE 1. DESCRIPTIVE STATISTICS OF LABORATORY PARAMETERS IN 5672 PATIENTS WITH TRAUMATIC BRAIN INJURY

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Glucose (mMol/L)</th>
<th>Sodium (mMol)</th>
<th>PH</th>
<th>Platelets (10^9/L)</th>
<th>Pro-thrombin time (sec)</th>
<th>Hb (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%) available</td>
<td>Median (25–75p)</td>
<td>N (%) available</td>
<td>Median (25–75p)</td>
<td>N (%) available</td>
<td>Median (25–75p)</td>
<td>N (%) available</td>
</tr>
<tr>
<td>TCDB</td>
<td>604</td>
<td>384 (64)</td>
<td>139 (136–142)</td>
<td>544 (90)</td>
<td>7.38 (7.30–7.45)</td>
<td>243 (40)</td>
<td>240 (181–299)</td>
</tr>
<tr>
<td>HIT I</td>
<td>350</td>
<td>334 (95)</td>
<td>139 (136–142)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>339 (97)</td>
</tr>
<tr>
<td>TIUS</td>
<td>1042</td>
<td>997 (96)</td>
<td>139 (136–142)</td>
<td>856 (82)</td>
<td>7.38 (7.30–7.45)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>TINT</td>
<td>1121</td>
<td>1104 (98)</td>
<td>139 (136–142)</td>
<td>850 (76)</td>
<td>7.39 (7.33–7.45)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>SKB</td>
<td>126</td>
<td>124 (98)</td>
<td>139 (137–141)</td>
<td>126 (100)</td>
<td>7.38 (7.30–7.45)</td>
<td>17 (93)</td>
<td>178 (138–2322)</td>
</tr>
<tr>
<td>SAP</td>
<td>919</td>
<td>880 (96)</td>
<td>140 (138–143)</td>
<td>0 (0)</td>
<td>830 (90)</td>
<td>163 (127–201)</td>
<td>831 (90)</td>
</tr>
<tr>
<td>Overall</td>
<td>5672</td>
<td>5270 (93)</td>
<td>140 (137–142)</td>
<td>3398 (60)</td>
<td>7.39 (7.32–7.45)</td>
<td>1629 (29)</td>
<td>195 (147–255)</td>
</tr>
</tbody>
</table>

*The summary data presented as overall are simple totals rather than any more sophisticated pooled estimate.*
stronger for points of dichotomization for the GOS closer to death/vegetative (Table 3), but consistent across studies (Fig. 3). Prothrombin time showed a strong prognostic effect in the TCDB and PEGSOD studies, but not in the SKB study (p for heterogeneity was <0.01). Hyponatremia was associated with poorer outcome, but the prognostic effect of hypernatremia was weak and only significant for the split for dichotomization between the categories severe disability and vegetative. The results of proportional odds analysis confirmed the results of the binary analyses. On multivariable analysis, adjusting for age, motor score, and pupils, the prognostic effects for all laboratory parameter except sodium remained substantial or even increased (Table 3).

Associations with Other Variables

Multiple associations between laboratory values and other variables were identified, but these associations were generally weak. Low values for Hb and platelets were associated with lower systolic blood pressure (Fig. 4). A change point was noted at a systolic blood pressure of approximately 140 mm Hg. Lower pH values were found in patients who had suffered hypotension and/or hypoxia prior to admission (Fig. 5). Glucose levels were also strongly related to age (Fig. 6), but the prognostic effect of glucose remained following adjustment for age (OR: 1.62). No clear associations were noted between glucose and clinical severity, as determined by the motor score.

DISCUSSION

This study confirmed the predictive value of various laboratory parameters routinely recorded on admission following TBI. A striking finding was that, except for sodium, a continuous and approximately linear relation to outcome was present across ranges of normal and abnormal values. Threshold values could not be identified.

The clinical value of predictors is determined by their reliability (observer agreement) on assessment, the prevalence of abnormalities and the strength of the prognostic effect (odds ratio). The laboratory parameters that we considered are standardized between laboratories and hence objective and reliable. The prevalence of abnormal values was low for platelets, but substantial for the other laboratory parameters investigated. The strongest predictive effect was observed for glucose and Hb. Multiple associations between laboratory parameters and between laboratory values and clinical parameters were observed, but prognostic effects remained substantial following adjusted analysis (Murray et al., 2006). Consequently, laboratory parameters are of considerable prognostic relevance in TBI.

Glucose

The majority (82%) of the patients included in our study had elevated glucose levels. Stress hyperglycemia is a common finding in critical care patients (Cely et al., 2004) and is considered part of a systemic response triggered by an increase in counter regulatory hormones such as cortisol (Khani and Tayek, 2001), glucagon (Hill and McCallum, 1991), catecholamines (Watt et al., 2001), and cytokines (Flores et al., 1990; Sakurai et al., 1996). Elevated cytokine levels can induce insulin resistance, leading to a decrease in glucose transportation. Hyperglycemia may be further exacerbated by intravenous administration of glucose and drugs (catecholamines, steroids) or triggered directly by neuronal injury. Hyperglycemia is associated with poorer outcome across the different disease entities treated in intensive care units, including acute myocardial infarction (Capes et al., 2000; Norhammar et al., 1999) and stroke (Capes et al., 2001). Many studies in TBI have also reported a relation between hyperglycemia and poor outcome (Pentelenyi and Kammerer, 1977; Michaud et al., 1991; Margulies et al., 1994; Yang et al., 1995; Lanno et al., 2000; Paret et al., 1999; Walia and Sutcliffe, 2002; Díaz-Parejo et al., 2003; Glenn et al., 2003; Cochran et al., 2003; Rovlias and Kotsou, 2000, 2004; Zygun et al., 2004). Threshold values of 11.1 mmol/L (Lam et al., 1991; Young et al., 1989; Rovlias and Kotsou, 2004) or higher (Pentelenyi and Kammerer, 1977; Deloof et al., 1979; Merguerian et al., 1981) have been described. Our studies, however, re-
FIG. 1. Relationships of laboratory parameters to outcome at 6 months. The lowest line (solid) indicates the probability of mortality (GOS 1), the second the combination of mortality and vegetative outcome (GOS 1, 2, or 3), and the fourth line the probability of less than good outcome (GOS < 5). Relationships were analyzed with spline functions in logistic regression models. The distribution of laboratory values is depicted at the bottom of each graph.
FIG. 2. Distribution of laboratory parameters by GOS at 6 months. The boxplots show the median values and 25–75 percentile in a box, and 2.5–97.5 percentiles between whiskers, for the GOS grouped into three categories.
### Table 3. Associations of Laboratory Parameters with Glasgow Outcome Scale (GOS) at Six Months after Traumatic Brain Injury

<table>
<thead>
<tr>
<th></th>
<th>Glucose (N = 4831)</th>
<th>Sodium low/high (N = 5267)</th>
<th>pH (N = 3395)</th>
<th>Platelet (N = 1629)</th>
<th>PT (N = 840)</th>
<th>Hb (N = 3872)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dichotomous OR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than good vs. good recovery</td>
<td>1.57 (1.45–1.70)</td>
<td>1.32 (1.12–1.56)</td>
<td>0.83</td>
<td>0.74</td>
<td>1.16</td>
<td>0.72</td>
</tr>
<tr>
<td>Unfavorable vs. favorable outcome</td>
<td>1.69 (1.52–1.89)</td>
<td>1.43 (1.24–1.65)</td>
<td>0.83</td>
<td>0.67</td>
<td>1.42</td>
<td>0.66</td>
</tr>
<tr>
<td>Death/vegetative vs. conscious survival</td>
<td>1.80 (1.61–2.00)</td>
<td>1.51 (1.30–1.75)</td>
<td>0.78</td>
<td>0.69</td>
<td>1.66</td>
<td>0.69</td>
</tr>
<tr>
<td>Death vs. alive</td>
<td>1.85 (1.70–2.01)</td>
<td>1.35 (1.12–1.62)</td>
<td>0.73</td>
<td>0.65</td>
<td>1.64</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Proportional OR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted</td>
<td>1.68 (1.54–1.83)</td>
<td>1.40 (1.22–1.60)</td>
<td>0.80</td>
<td>0.70</td>
<td>1.41</td>
<td>0.69</td>
</tr>
<tr>
<td>Adjusted for age, motor score, and pupilsa</td>
<td>1.45 (1.36–1.55)</td>
<td>1.14 (0.96–1.43)</td>
<td>0.84</td>
<td>0.79</td>
<td>1.63</td>
<td>0.76</td>
</tr>
</tbody>
</table>

aExcluding children <14 years of age.

Odds ratio (OR) is calculated for GOS dichotomized as less than good recovery (D/V/SD/MD vs. GR), unfavorable outcome (D/V/SD vs. MD/GR), death/vegetative versus conscious survival (D/V vs. SD/MD/GR) and death versus survival, as well as with a proportional odds model, with their 95% confidence intervals. Odds ratios refer to the comparison of lab values at the 75th percentile versus the 25th percentile, except for sodium, where comparisons are between categories of low (<25th percentile) and high (>75th percentile) values versus a category of middle values (25th to 75th percentile).
FIG. 3. Forest plots demonstrating the consistency in the strength of the associations between six laboratory parameters and outcome across the studies.
porting on much larger numbers, show a continuous relation between hyperglycemia and outcome.

Sodium

Our findings that both hypo- and hypernatremia are associated with poorer outcome are particularly relevant in relation to the recent surge in interest in the use of hypertonic saline both for small volume resuscitation and for treatment of raised ICP (Ogden et al., 2005). In neurocritical care, interest has mainly focused on hyponatremia, which may exacerbate the development of brain edema. We found that hyponatremia is a relatively infrequent occurrence on admission following TBI, but that it is associated with poorer outcome. To our knowledge no studies have previously specifically addressed the relation between sodium levels on admission and outcome following TBI. Electrolyte disturbances occur frequently in TBI patients in the ICU setting (59.3%) but were not found to be independently associated with unfavorable outcome (Piek et al., 1992). Neither was a relation found between elevated extracellular sodium levels determined with microdialysis and poorer outcome (Alessandri et al., 1998).

We found a weak relation between hypernatremia and outcome, which was primarily related to mortality. The databases included in our study pre-date the general use of hypertonic saline. Consequently, it is uncertain whether this association also may hold when hypernatremia results from the use of hypertonic saline. In a randomized controlled trial on the pre-hospital use of hypertonic saline (Cooper et al., 2004) described high plasma sodium levels of 149 (SD 3.7) mEq/L, but found no clear effect on outcome. Nevertheless, we consider this an important issue requiring further study.

pH

Low arterial pH on admission in TBI may be seen as a marker of sustained secondary insults, reflecting either actual or recently sustained hypoventilation with concomitant hypoxia, or systemic acidosis following hypotension. We consider pH to be less sensitive to effects of early resuscitation and stabilization than arterial pO2 or pCO2. On admission of severe TBI patients the first priority is to ensure adequate respiration (ventilation) and to obtain hemodynamic stability. Consequently, arterial blood gasses are usually only drawn after the primary stabilization. pH levels below normal values were observed in 34% of patients. The occurrence of abnormal values was strongly associated with episodes of hypoxia and/or hypotension. However, pH was also related to poorer outcome across the range of normal values. The relation between arterial pH and outcome has not been the subject

![FIG. 4.](image1.png) (A) Spline function analysis summarizing the association between hemoglobin and systolic blood pressure. Graph represents the “best fit” curve, but we note that a wide scatter of Hb values was present over the ranges of systolic blood pressure. (B) Spline function demonstrating the association between platelets and systolic blood pressure. Graph represents the “best fit” curve, but we note that a wide scatter of platelet levels was present over the ranges of systolic blood pressure.

![FIG. 5.](image2.png) The boxplots show the median and 25/75% ranges for pH and the 2.5/97.5% between whiskers.
of previous studies, but relations have been reported between brain tissue pH, pH in the jugular venous blood, and outcome (Kushi et al., 1999; Li et al., 2001).

**Hemoglobin**

In acute TBI, low hemoglobin may result from blood loss or excessive fluid administration. As a consequence, the oxygen carrying capacity of the blood is decreased, potentially increasing the risk for secondary ischemic damage at a time when cerebral blood flow is already compromised. High Hb levels however, will increase viscosity and compromise perfusion. Theoretically a U-shaped relation between Hb and outcome might therefore be expected. We found a continuous linear relation. It should however be noted that high levels of Hb were observed very seldom, and the possibility of poorer outcome at Hb levels above the ranges observed cannot be excluded. Abnormally low Hb values were observed in a substantial number of patients (17%) and associated with other parameters (e.g., hypotension). Anemia is a common problem in critically ill patients and its association to poorer outcome documented for many disease entities (du Cheyron et al., 2005; Hebert et al., 1997) including TBI (Sanchez-Olmedo et al., 2005).

**Coagulopathy**

The importance of coagulopathy in TBI is being increasingly recognized (Stein et al., 1992; Stein and Smith, 2004; Selladurai et al., 1997; Oertel et al., 2002). The pathophysiology however is complex: blood loss due to systemic or cranial trauma may induce hemorrhagic diathesis by depletion of platelet and clotting factors. In contrast, the brain injury may induce a hypercoagulation state, either systemically or locally in the penumbra of a contusion by release of a pro-coagulant tissue factor. Increased plasma concentrations of fibrin/fibrinogen degradation products (FDP) and plasmin–α2–plasmin inhibitor and decreased fibrinogen levels are associated with a higher percentage of unfavorable outcome after injury (Olson et al., 1989; Selladurai et al., 1997). A hypercoagulable state has been reported in up to 76% of patients with severe traumatic brain injury and various series report an incidence of full blown disseminated intravascular coagulation in 15–40% of patients (Bredbacka and Edner, 1994; Hoots, 1997; Miner et al., 1982; Stein et al., 1992). The incidence of local cerebral intravascular coagulation is even higher (Stein et al., 2002). Various studies (Kaufman et al., 1980; Miner et al., 1982; Stein et al., 1992) have demonstrated a relation between coagulopathy and poorer outcome in TBI. We found prognostic effects of prothrombin time and platelets. These findings are in agreement with previous studies (Kearney et al., 1992; Hymel et al., 1997). Hymel et al. (1997) found more severe prothrombin time prolongations in patients dying and further showed that PT prolongations occur more frequently (54%) in patients with parenchymal brain damage than in those without parenchymal damage (20%). A limitation of our study is that we could not analyze the coagulation status of individual patients in detail and were restricted to investigations of platelets and prothrombin time. However, our findings emphasize the importance of the occurrence and correction of coagulopathic syndromes.

**Therapeutic Implications**

In contrast to most clinical and radiological parameters, laboratory parameters are amenable to treatment and our results may motivate more aggressive correction of abnormal values.

The frequent occurrence of hyperglycemia in ICU patients, the demonstrated relation to outcome and the realization that hyperglycemia is a cause of secondary damage, has triggered studies in critical care medicine to investigate whether more intensive management of hyperglycemia with insulin treatment might improve outcome. van den Berghe et al. (2001) reported a reduction in ICU mortality with this approach. To our knowledge, no studies have directly addressed the benefits of more intensive management of hyperglycemia in TBI, but extrapolation of the experiences in general critical care to TBI may be appropriate. This concept is supported by our findings of a continuous relation between glucose and outcome in TBI. Particular care is however required to prevent insulin overdose and subsequent hypoglycemia as this may have even more detrimental effects on the injured brain.

As with glucose, Hb is a parameter which can be readily modified by treatment. Generally accepted principles are only to give blood transfusions in the ICU if Hb lev-
els fall below 7 g/dL, but more recent insight favors initiation of blood transfusion in acutely injured patients at less depressed levels of hemoglobin (Goodnough and Bach, 2001). The continuous relation observed in our studies similarly supports the concept for earlier institution of blood transfusion in TBI patients. This may not only be appropriate in the acute phase, but also in post acute treatment, as anemia has been shown to be a risk factor for transfer of TBI patients back to the acute care facility from in patient rehabilitation (Deshpande et al., 1997). Studies to evaluate the effect of earlier institution of blood transfusions and correction of Hb on cerebral oxygenation and blood flow should be considered. This concept is supported by results from a small cohort study (Smith et al., 2005), describing a 49% mean increase in brain tissue oxygen tension following red blood cell transfusions.

The prognostic effects of prothrombin time and platelets as found in our studies, and the increased realization of the importance of coagulopathy in TBI would indicate the necessity to focus our attention more on the occurrence and correction of coagulopathic syndromes. Furthermore, lesion progression and secondary deterioration are more frequent in the presence of coagulopathy.

CONCLUSION

We conclude that laboratory parameters, routinely determined on admission, are important predictors of outcome after TBI. The presence of coagulopathy, hyperglycemia, and anemia are unequivocally related to poorer outcome. Although the presence of these insults may in part be a marker of injury severity, we consider these parameters candidates for therapeutic evaluation preferably in the form of randomized clinical trials. We envisage a trial evaluating more aggressive correction of hyperglycemia and anemia and studies evaluating the benefits of early correction of investigatory syndromes. Such trials or studies should adjust for the heterogeneity in the patient population, a specific characteristic of TBI, and utilize the ordinal nature of the GOS in the primary efficacy analysis.

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REFERENCES


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