Optimising diagnosis and treatment of coagulopathy in severely injured trauma patients

Balvers, K.

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HAEMOGLOBIN LEVEL AND NEUROLOGIC OUTCOME IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY


Submitted
ABSTRACT

Introduction: A low haemoglobin (Hb) level in patients with traumatic brain injury (TBI) may worsen neurologic outcome. The aim of this study was to test the hypothesis that low Hb levels are associated with poorer neurologic outcomes in TBI patients.

Methods: A post-hoc analysis of the prospective multicentre study was performed on subjects recruited in 4 level-1 trauma centres. Adult trauma patients with traumatic brain injury (AIS head ≥3), ICU admission and available Hb levels on admission were eligible. The primary outcome was the neurologic outcome on discharge.

Results: A total of 258 TBI patients were included. After adjustment for the confounders age, gender and the number of red blood cell units transfused in 24 hours, a lower Hb level was significantly associated with a poorer neurologic outcome (OR 0.88, 95% CI 0.78-0.99, p=0.048).

Conclusion: A lower Hb level is associated with a poorer neurologic outcome in TBI patients. In particular, awareness is required in multi-traumatized TBI patients with low Hb levels. Randomized controlled trials are required to confirm whether maintenance of higher Hb levels improves neurologic outcome in TBI patients.
INTRODUCTION

Anaemia is frequently observed in patients with traumatic brain injury (TBI)\(^1\),\(^2\) and is associated with an increased mortality\(^1\),\(^3\)\(^-\)\(^5\). Anaemia hampers adequate cerebral oxygenation, which induce cerebral oedema and an increased intracranial pressure\(^6\)\(^-\)\(^8\). Transfusion of red blood cells (RBCs) is associated with increased haemoglobin (Hb) levels and an improved brain tissue oxygenation\(^9\),\(^10\). Therefore, transfusion of RBCs may be appropriate in TBI patients in order to maintain higher Hb levels and to improve neurological outcome. However, transfusion of RBCs is also associated with adverse events\(^11\)\(^-\)\(^13\). Clear evidence for a beneficial effect of higher Hb levels on outcome in TBI patients is therefore required.

The majority of previous studies investigating the association between Hb levels and outcome in trauma patients have used mortality as a primary endpoint. Given the relation between anaemia and cerebral performance,\(^9\),\(^10\) neurologic recovery may also be a relevant endpoint, and has indeed been used as primary outcome in a recent Hb threshold trial in TBI patients\(^5\). However, the number of studies investigating the association between Hb levels and neurologic outcome in TBI patients is small and studies have yielded contradicting results\(^3\),\(^5\),\(^14\)\(^-\)\(^16\). The aim of this study was to test the hypothesis that low Hb levels are associated with poorer neurologic outcomes in TBI patients.

MATERIALS AND METHODS

This study is a post-hoc analysis of the ongoing Activation of Coagulation and Inflammation in Trauma study (ACIT, United Kingdom Clinical Research Network Study Portfolio, ID: 5637), which is a prospective observational multicentre study on coagulopathy in trauma.

Subjects were recruited between January 2008 and December 2014 in 4 European level-1 trauma centres; London, Oxford, Oslo and Amsterdam. All adult trauma patients (age≥18 years) who met the local criteria for highest trauma team level activation were enrolled. Exclusion criteria of the ACIT study were age <18 years old, arrival in the emergency department more than 2 hours after injury as well as transfer from another hospital, transfusion of more than 2000 mL of intravenous fluids prior to Emergency Department (ED) arrival and burns covering more than 5% of the total body surface area. Patients were retrospectively excluded if they declined to give informed consent, were found to be taking anticoagulant medications other than aspirin (<650mg/day), or had moderate or severe liver disease (Child’s classification B or C3) or a known bleeding diathesis.
Of the patients included in the ACIT study, all patients who suffered from severe traumatic brain injury with an AIS head ≥ 3, were admitted to ICU and had admission Hb levels available were selected for analysis. Written informed consent was obtained from each patient and healthy individual. When the patient was unconscious, written informed consent was obtained from a legal representative. This study was performed after approval by the local ethics committees.

DATA COLLECTION

Data on patient demographics; time of injury; mechanism (blunt or penetrating); comorbidities; baseline vital signs and injury severity classified using the Injury Severity Score (ISS); Abbreviated Injury Score (AIS); presence of shock during resuscitation; transfusion requirements; laboratory tests during the first 72 hours and requirement of early operative intervention (neurosurgical and other surgical interventions), ICU length of stay, GCS at discharge from ICU, hospital length of stay and 28-day mortality were collected prospectively. Hb levels were collected on hospital admission and 24 hours post-injury. The lowest Hb level within 24 hours was used to define the association between the Hb level and neurologic outcome. A subgroup analyses on isolated TBI patients was also performed. Isolated TBI was defined as an AIS head of ≥ 3 and an AIS in other regions <3.

OUTCOME MEASURES

The primary outcome of this study was the neurologic outcome of the patients post-injury. The neurologic outcome was retrospectively defined by the Glasgow Coma Scale (GCS) on ICU discharge and the discharge location (usual place of residence, nursing/rehabilitation facility or died). The neurologic outcome was dichotomized, in which a severe disability, a vegetative state or dead were termed as poor neurologic outcome (GCS on ICU discharge ≤ 8). Good recovery or moderate disability was termed as good neurologic outcome (GCS on ICU discharge ≥ 14). Of note, all patients who went home irrespective of their GCS, were scored as good neurologic outcome, whereas all patients who died were scored as poor neurologic recovery. Patients with a GCS on ICU discharge of 13 or less and a discharge location other than the usual place of residence were scored as a poor neurologic outcome. However, patients who were discharged to a nursing or rehabilitation facility to recover from severe injury other than from traumatic brain injury, were scored as good neurologic recovery.
STATISTICAL ANALYSIS

Continuous normally distributed variables will be expressed by their mean and standard deviation or when not normally distributed as medians and their interquartile ranges. Categorical variables will be expressed as n (%). To test groups Student’s t-test will be used, if continuous data is not normally distributed the Mann-Whitney U test will be used. Categorical variables will be compared with the Chi-square test or Fisher’s exact tests.

The goal of the primary analysis was to quantify the relationship between Hb levels at admission on the emergency department and the neurologic outcomes in TBI patients, controlling for other variables17. We identified potential predictors of neurologic outcome by univariable logistic regression. From the univariate logistic regression, all potential confounders were selected that showed a p value of less or equal to 0.10 or where possibly otherwise clinically relevant to be included within the final multiple logistic regression model. Confounding was defined as ≥ 10% change in the coefficient of the central determinant (Hb level) as a consequence of adding a covariate. The added covariates in the final model were tested for linearity assumption18. Confounders included in the analyses were trauma mechanism, gender, age, intubation, AIS head/neck, systolic blood pressure (SBP) on ED, GCS on ED and the number of transfused red blood cells (RBCs) in 24 hours3, 15, 16. Statistical significance was considered to be a p< 0.05, whether appropriate statistical uncertainty was expressed by the 95% confidence levels. Statistical analyses were performed in SPSS version 21(IBM, Chicago, IL, USA).

RESULTS

In total 2760 severely injured trauma patients met the ACIT study inclusion criteria. Of these 2760 patients, 215 patients were excluded retrospectively as patients declined to give consent or due to retrospective exclusion criteria. Of the remaining 2545 patients, 258 patients suffered from severe traumatic brain injury with an AIS head ≥3, were admitted to ICU, had admission Hb levels available and were eligible for this study. A total of 112 patients (43%) were diagnosed with isolated TBI. The mean age was 43 ±19 years, of which the majority was male (74%). Patients were severely injured with an ISS of 30 (±12), a GCS on the ED of 7 (3-13) and a lowest Hb measured within 24 hours of 10.8 (±2.4) g/dL. The overall mortality on 28-days was 30% (Table 1).
The neurologic outcome as defined by the GCS on ICU discharge and discharge location is displayed in Table 2. Data on ICU discharge location were not obtained in 7 patients. Of the remaining 252 TBI patients, 93 patients (37%) were diagnosed with poor neurologic recovery, 44 patients (17%) with moderate neurologic recovery and 115 patients (46%) with moderately good neurologic recovery on ICU discharge. Of the patients with poor neurologic recovery, 85 patients (91%) died or were discharged to a nursing or rehabilitation facility and had a poor neurologic outcome. Of the patients with moderate neurologic recovery, 35 patients (25%) were discharged to a nursing or rehabilitation facility to recover from severe injury other than traumatic brain injury. These patients were diagnosed as a good neurologic outcome.

**TABLE 2:** Neurologic outcome as defined by the GCS on ICU discharge and the discharge location.

<table>
<thead>
<tr>
<th>GCS</th>
<th>Home</th>
<th>Nursing facility/Rehabilitation facility</th>
<th>Dead</th>
<th>Poor neurologic recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤8</td>
<td>8 (9)</td>
<td>16 (17)</td>
<td>69 (74)</td>
<td>85 (91)</td>
</tr>
<tr>
<td>9-13</td>
<td>9 (20)</td>
<td>31 (70)</td>
<td>4 (9)</td>
<td>35 (80)</td>
</tr>
<tr>
<td>14-15</td>
<td>59 (52)</td>
<td>53 (37)</td>
<td>2 (1)</td>
<td>24 (21)</td>
</tr>
</tbody>
</table>
**Hb level and neurologic outcome**

In total 144 TBI patients had a poor neurologic outcome. In Table 3 the association between neurologic outcome and potential confounders are shown. Besides the Hb level, the GCS on admission and the AIS head were significantly associated with a poor neurologic outcome in the univariable logistic regression analysis (Table 3). However, after adding the covariates to the final multivariable logistic regression model, only age, gender and the number of RBCs transfused in 24 hours changed the coefficient of the Hb level with ≥10% and were considered as relevant confounders. After adjustment for these confounders, the Hb level was significantly associated with neurologic outcome (OR 0.88, 95% CI 0.78-0.99, p=0.048, Table 4). The OR of 0.88 expresses a 12% change in outcome as a result of an increase in the Hb level of 1 g/dL. An increase in the Hb level is therefore associated with a better neurologic outcome in TBI patients.

**Isolated TBI patients**

In comparison with non-isolated TBI patients, isolated TBI patients were less severely injured, less acidotic, less coagulopathic and were less frequently administered with blood products (Table 1). In the group with isolated TBI patients, patients with lower Hb levels were sicker than patients with high Hb levels. In the group of isolated TBI patients no significant association was observed between the Hb level and neurologic outcome in isolated TBI patients. Only a trend towards a better neurologic outcome was observed (OR 0.854 95% CI 0.712-1.025, p=0.090).

**TABLE 3**: Univariate analysis of the association between GCS outcome and the primary determinant and candidate confounding variables

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>Upper limit</th>
<th>Lower limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb ED*</td>
<td>0.85</td>
<td>0.76</td>
<td>0.95</td>
<td>0.004</td>
</tr>
<tr>
<td>Age, years</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>0.499</td>
</tr>
<tr>
<td>Gender, male</td>
<td>0.91</td>
<td>0.48</td>
<td>1.72</td>
<td>0.782</td>
</tr>
<tr>
<td>Intubated, yes</td>
<td>1.36</td>
<td>0.64</td>
<td>2.85</td>
<td>0.417</td>
</tr>
<tr>
<td>Trauma mechanism, blunt</td>
<td>0.81</td>
<td>0.27</td>
<td>2.54</td>
<td>0.704</td>
</tr>
<tr>
<td>Systolic blood pressure*</td>
<td>1.00</td>
<td>0.99</td>
<td>1.01</td>
<td>0.694</td>
</tr>
<tr>
<td>GCS on admission</td>
<td>0.83</td>
<td>0.77</td>
<td>0.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>AIS head</td>
<td>2.45</td>
<td>1.66</td>
<td>3.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Isolated TBI</td>
<td>1.34</td>
<td>0.76</td>
<td>2.41</td>
<td>0.314</td>
</tr>
<tr>
<td>Number RBCs within 24 hr</td>
<td>1.05</td>
<td>1.00</td>
<td>1.12</td>
<td>0.084</td>
</tr>
</tbody>
</table>

*Vital signs and laboratory tests on Emergency Department
DISCUSSION

Our findings indicate that TBI patients with lower Hb levels are at risk of developing a poor neurologic outcome. In particular, awareness for a poor neurologic outcome is required in multi-traumatized TBI patients with low Hb levels.

Haemoglobin level

The association between the Hb level and neurologic outcome has been explored in a small number of studies and results are inconsistent\(^3\,5\,14-16\). The reasons for this inconsistency vary. Studies tend to be single-centre retrospective studies with small sample sizes, the majority of the studies used mortality as a primary outcome and various cut-off values have been used ranging from a Hb level of ≤7 to ≤10 g/dL\(^3\,5\,15\,19\,20\).

In this study we have tried to address some of these limitations. Using a continuous parameter for the Hb level may provide more detailed information than cut-off values. Furthermore, we have performed a post-hoc analysis of multicentre prospectively collected data.

Previous observational studies observed that higher Hb or hematocrit levels were associated with improved long-term outcomes\(^3\,16\). However, results of a recent transfusion trial in TBI patients reported conflicting results\(^5\). No difference in neurologic outcome was found comparing transfusion thresholds of 7 g/dL and 10 g/dL. In our study we found that lower Hb levels predicted poor neurologic outcome in TBI patients fairly. This suggests that higher Hb levels may contribute to higher arterial oxygen content and subsequently to a higher cerebral oxygen delivery, which is in line with basic science work done in this field\(^6\,8\). Although the findings observed in this study are in accordance with results of previous observational studies, results are in contrast to the results found in the randomized transfusion trial. An explanation for the differences in results may be that, although the randomized transfusion trial was of a very high quality, the primary aim of this study was to investigate the effect of erythropoietin on neurologic recovery after traumatic brain injury, and may to some extent have biased

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>Upper limit</th>
<th>Lower limit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb level</td>
<td>0.85</td>
<td>0.76</td>
<td>0.95</td>
<td>0.004</td>
</tr>
<tr>
<td>Hb, corrected for Age</td>
<td>0.87</td>
<td>0.77</td>
<td>0.97</td>
<td>0.013</td>
</tr>
<tr>
<td>Hb, corrected for Age, Gender</td>
<td>0.86</td>
<td>0.76</td>
<td>0.96</td>
<td>0.010</td>
</tr>
<tr>
<td>Hb, corrected for Age, Gender, RBCs in 24 hr</td>
<td>0.88</td>
<td>0.78</td>
<td>0.99</td>
<td>0.048</td>
</tr>
</tbody>
</table>

TABLE 4: Association between the Hb level and neurologic outcome. Table displays the crude univariable association and the multivariable adjusted association for confounding.
we found no significant association between the Hb level and poor neurologic outcome in patients with isolated TBI. Isolated TBI patients were less injured than non-isolated TBI patients. Additionally, despite the fact that Hb levels were not significantly different between both groups, polytrauma patients with TBI received significantly more blood products than isolated TBI patients. This suggests that blood loss was more severe in multi-traumatized TBI patients, which resulted in a reduced cerebral oxygenation and a poorer neurologic outcome. However, large randomized controlled trials in TBI patients are required to further investigate the association between low Hb levels and neurologic outcome.

Limitations to this study should be acknowledged. A substantial proportion of patients in this study presented with multi-trauma and heterogeneity in our study population was therefore considerable. Furthermore, we used a retrospectively defined neurologic outcome as primary outcome and this post-hoc analysis of prospectively collected data may have missed confounders unaccounted for. Also, due to strict inclusion criteria, results do not hold for those patients on anticoagulation as these were excluded in this study and time of transfusion was not registered. Additionally, it was not feasible to investigate the association between Hb levels lower than 9 g/dL and neurologic outcome, as this was hampered by small patient numbers. Lastly, the cause of death was not documented systematically in this study.

In summary, we have documented the association between low Hb levels and poor neurologic outcome in TBI patients. In particular, awareness is required in multi-traumatized TBI patients with low Hb levels. Randomized controlled trials are needed to assess whether maintenance of higher Hb levels improve functional outcome in TBI patients.
REFERENCES


REFERENCES
