Coagulation factor levels in neurosurgical patients with mild prolongation of prothrombin time: effect on plasma transfusion therapy

Clinical article

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Object. Neurosurgical patients often have mildly prolonged prothrombin time (PT) or international normalized ratio (INR). In the absence of liver disease this mild prolongation appears to be due to the use of very sensitive PT reagents. Therefore, the authors performed relevant coagulation factor assays to assess coagulopathy in such patients. They also compared plasma transfusion practices in their hospital before and after the study.

Methods. The authors tested 30 plasma specimens from 25 patients with an INR of 1.3–1.7 for coagulation factors II, VII, and VIII. They also evaluated plasma orders during the 5-month study period and compared them with similar poststudy periods following changes in plasma transfusion guidelines based on the study results.

Results. At the time of plasma orders the median INR was 1.35 (range 1.3–1.7, normal reference range 0.9–1.2) with a corresponding median PT of 13.6 seconds (range 12.8–17.6 seconds). All partial thromboplastin times were normal (median 29.0 seconds, range 19.3–33.7 seconds). The median factor VII level was 57% (range 25%–124%), whereas the hemostatic levels recommended for major surgery are 15%–25%. Factors II and VIII levels were also within the hemostatic range (median 72% and 118%, respectively). Based on these scientific data, plasma transfusion guidelines were modified and resulted in a 75%–85% reduction in plasma orders for mildly prolonged INR over the next 2 years.

Conclusions. Neurosurgical patients with a mild prolongation of INR (up to 1.7) have hemostatically normal levels of important coagulation factors, and the authors recommend that plasma not be transfused to simply correct this abnormal laboratory value. (DOI: 10.3171/2010.7.JNS091699)

Key Words • prothrombin time • international normalized ratio • coagulation factor • plasma • transfusion

HEMOSTASIS is a complex interaction among 1) the fluid phase of procoagulants that generate thrombin, 2) the natural anticoagulants that regulate thrombin, 3) the fibrinolytic system that controls the size of thrombus and maintains vascular patency, and 4) the cellular phase that includes platelets and endothelium. To date, no single global test exists to assess these 4 components of hemostasis. The in vitro coagulation tests, the PT and PTT, were developed to identify the cause of bleeding in a symptomatic bleeding patient; they have never been shown to assess the risk of bleeding in a nonbleeding patient.16,20,35

Because different sensitivities of tissue thromboplastin reagents account for the variability of PT, the INR was introduced to monitor warfarin therapy. The INR is a calculated value derived by the following formula: (patient PT/mean normal PT)×ISI, where ISI is a value assigned to the PT reagent when compared with a WHO reference standard with an ISI of 1.0.31,43,44 The INR was standardized on plasmas from patients on chronic warfarin therapy that affects only VKD factors II, VII, IX, and X. Use of the INR is therefore inappropriate in other medical conditions in which clotting factors other than VKD factors are affected.10 However, the INR is often (mis)used in clinical practice to assess hemostasis in patients not receiving warfarin therapy; thus, patients with mildly elevated INRs are reflexively transfused with FFP, usually perioperatively.

In the past, less-sensitive thromboplastin reagents (ISI > 2.0) caused a prolonged PT only when factor VII
was < 30%. With the older reagents, clinicians were accustomed to a PT value 1.5 times the normal value as indicative of a significant coagulopathy such as that due to disseminated intravascular coagulation, liver disease, or therapeutic warfarin. Today, very sensitive thromboplatin reagents (ISI approximately 0.9–1.2) are used for PT; therefore, PT is prolonged even when factor VII values are 40%–45%, well above the recommended hemostatic level for surgical procedures, that is, 15%–25%. An INR calculated with an ISI of 1.0 for a PT of 16.5 seconds is only 1.5 compared with an INR of 2.1 when the reagent ISI is 2.0. This PT value of 16.5 seconds (1.5 times normal) is believed by many clinicians to indicate coagulopathy. The result has most probably been an increase in the number of plasma transfusions since the late 1990s and can be primarily attributed to laboratory failures to educate clinicians as regards significant changes in PT reagents.

The majority of transfusion-related deaths occur after the transfusion of a single unit of plasma. Yet each year approximately 3 million plasma units are transfused in the US despite the questionable effectiveness of this therapy. Among the numerous potential adverse complications of a plasma transfusion are transfusion-associated circulatory overload, allergic reactions, and transfusion-related acute lung injury, the number 1 cause of transfusion-related death in the US. A mild elevation of PT is observed in many neurosurgical patients. Since there is a paucity of data on coagulation factor levels in patients with mild elevations of PT or INR, we evaluated relevant clotting factors (II, VII, and VIII) in neurosurgical patients. We also compared the plasma transfusion practices in our hospital before and after the study.

Methods

Patient Population

Thirty-one neurosurgical patients (trauma or elective) with mildly elevated INRs (range 1.3–1.7, normal INR 0.9–1.2) were included in the study, which was conducted at the Parkland Memorial Hospital in Dallas, Texas. The local institutional review board approved the study.

Sample Collection

Within 8 hours of collection time, the coagulation (PT and PTT) blood specimen (in 3.2% sodium citrate) that triggered the request for plasma transfusions was retrieved from the laboratory. Plasma was separated and immediately frozen at −70°C pending further testing.

Factor Assays

Thirty plasma specimens from 25 patients were tested for coagulation factors II, VII, and VIII on an automated coagulation analyzer (BCS, Dade Behring). Factor VII was selected because it affects PT (INR) and has the shortest half-life (approximately 60 hours) of all VKD factors. Factor VIII was selected because it is an acute phase reactant and elevated factor VIII level is a well-known risk factor for thrombosis. Significantly increased factor VIII levels are reflected in a shortened PTT. None of the patients had evidence of liver disease.

Plasma Therapy

From the Transfusion Service’s computer information system, we retrieved information on the number of plasma units transfused for neurosurgery during the 5-month study period; we also captured the PT, INR, and PTT values 24 hours after plasma transfusion to evaluate its effect. We instituted new plasma administration guidelines based on study results and then compared plasma use in neurosurgical patients with an INR of 1.3–1.6 during the study period with plasma use during a similar 5-month poststudy period. Plasma use was again evaluated at 1- and 2-year intervals poststudy.

Results

Thirty-six samples were collected from 31 patients; however, 6 samples from 6 patients were excluded from the study because 2 patients were on warfarin and the remaining 4 did not have neurosurgical diagnoses. Thus, 30 samples from 25 patients (5 patients had 2 separate samples each during the hospital stay) were included in the analysis. Table 1 shows patient demographics, and Table 2 lists the PT, INR, and PTT results. The median INR was 1.35 (range 1.3–1.7) with a corresponding median PT of 13.6 seconds (range 12.8–17.6 seconds). All PTTs were normal (median 29.0 seconds, range 19.3–33.7 seconds); 2 samples had shortened PTTs (19.3 and 20.9 seconds). Factors II, VII, and VIII levels are also featured in Table 2. All patients had factor VII ≥ 25%. Minimum values recommended for major surgery are 15%–25%. Factor II levels were also within the hemostatic range. Factor VIII levels were elevated in 11 samples (164%–547%), reflected by a PTT that was either short or at the lower end of normal.

During the initial 5-month study period, 99 requests for plasma transfusions for 69 patients with an INR of 1.3–1.7 were received in the Transfusion Service. A mean of 3 U of plasma (median 2 U, range 1–7 U) were transfused to 46 of 69 patients within the next 24 hours. During the 5 months after the implementation of new plasma transfusion guidelines, the Transfusion Service received only 15 requests for plasma for 14 patients with an INR of 1.3–1.7. Note, however, that only 2 of these patients were transfused with plasma within the next 24 hours (1 patient was status post–meningioma resection, and the other had stable traumatic intracranial hemorrhage following a motorcycle collision; neither of these 2 patients had active bleeding or worsening of intracranial hemorrhage), and 12 did not receive transfusions. The mean and median number of plasma units transfused was 2. The PT, INR, and PTT at the time of a plasma request and 24 hours posttransfusion are featured in Table 3. The INR values did not significantly change over 24 hours in both groups.
Coagulation factors in patients with mild prolongation of INR

TABLE 1: Summary of characteristics in 25 patients in whom plasma was obtained

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (M/F)</td>
<td>22:3</td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>43 ± 18</td>
</tr>
<tr>
<td>diagnosis</td>
<td></td>
</tr>
<tr>
<td>intracerebral hemorrhage</td>
<td>4</td>
</tr>
<tr>
<td>subdural hematoma</td>
<td>4</td>
</tr>
<tr>
<td>epidural hematoma</td>
<td>3</td>
</tr>
<tr>
<td>closed head injury</td>
<td>3</td>
</tr>
<tr>
<td>intracranial tumor</td>
<td>3</td>
</tr>
<tr>
<td>traumatic vertebral fracture/dislocation</td>
<td>3</td>
</tr>
<tr>
<td>open skull fracture</td>
<td>1</td>
</tr>
<tr>
<td>traumatic pneumoencephalus</td>
<td>1</td>
</tr>
<tr>
<td>arteriovenous malformation</td>
<td>1</td>
</tr>
<tr>
<td>intractable seizures</td>
<td>1</td>
</tr>
<tr>
<td>altered mental status</td>
<td>1</td>
</tr>
</tbody>
</table>

of patients (that is, those who were transfused with plasma and those who were not) and did not show significant statistical variation (p > 0.05).

Among 114 patients (study period and 5-month follow-up period), 33 patients underwent red blood cell transfusion (mean 2.9 ± 2 U, range 1–8 U) and 11 underwent platelet transfusion (mean 1.5 ± 0.8 U, range 1–4 U) during the 24 hours following plasma requests. In non-surgical patients at our institution, the transfusion trigger for red blood cells is a hemoglobin level ≤ 10 g/dL; and for platelet transfusion, < 100 × 10⁹/L. Two patients received cryoprecipitate for hypofibrinogenemia; 1 patient received one 10-pack dose, and one received two 10-pack doses.

Discussion

Our study showed hemostatically normal levels of important coagulation factors (II and VII) in patients with a mild elevation of INR (within 1.5 times the midnormal range). These results support the observation that there is no increase in the risk of bleeding in patients with PT or INR values within 1.5–1.8 times the midnormal range. In fact, many patients had elevated levels of factor VIII, conferring a transient hypercoagulable state despite the slightly prolonged INR. Moreover, there was no significant change in PT, INR, or PTT after plasma transfusions. Study results were presented during neurosurgery grand rounds. In the first 5 months after this presentation and the development of new plasma transfusion guidelines, there was an 85% reduction in plasma transfusion orders to correct mildly prolonged INR. During the corresponding 5-month periods 1 and 2 years later, the plasma requests for an INR of 1.3–1.6 remained low at 26% (26 requests over 5 months) and 15% (15 requests over 5 months), respectively, compared with the study period.

A recent retrospective study of ICP monitor placement in severe head injury patients with mild abnormality of the INR also showed no benefit of plasma therapy. In fact, the patients who received plasma therapy to correct the INR had significant delays (mean 19.2 hours) in ICP monitor placement as compared with those who did not get plasma (mean 8.8 hours, p < 0.002). Furthermore, not all patients with a moderately prolonged INR (> 1.7) had complete correction after receiving several units of plasma, and ICP monitors were placed with INRs > 1.3 in these patients. The study did not show an increase in the bleeding complication rates in patients with an INR of 1.3–1.6 with or without plasma, and the authors concluded that the data did not support plasma therapy for an INR ≤ 1.6.

Guidelines for plasma transfusion have been published by the American Association of Blood Banks, the British Committee for Standards in Haematology, and the College of American Pathologists, as well as for pediatric patients. These consensus guidelines list only a few clear-cut indications for plasma transfusion, including the treatment of thrombotic thrombocytopenic purpura, emergency reversal of vitamin K antagonists (prothrombin complex concentrate containing all VKD factors is the first choice), and treatment of bleeding due to multiple factor deficiencies as seen with trauma, disseminated intravascular coagulation, severe chronic liver disease, and so forth.

Holland and Brooks demonstrated that FFP transfusions in patients with an INR < 1.7 do not reliably reduce the INR; in fact, they expose patients to unnecessary risk. Even so, the use of FFP before procedures in patients with an elevated INR appears to be quite common. The use of plasma during the perioperative period has long been a controversial subject. Several trials comparing prophylactic plasma transfusion with other strategies were reported in patients undergoing cardiopulmonary bypass surgery. No studies have shown evidence of a perioperative plasma transfusion benefit. Five trials have compared a plasma group with a control group (no plasma) in patients undergoing cardiopulmonary bypass surgery. Five additional trials compared prophylactic perioperative plasma use with an artificial colloid solution such as Gelofusine, hetastarch, or albumin. None of these trials convincingly demonstrated that the prophylactic administration of a therapeutic dose of plasma reduced blood loss and red blood cell transfusion. Similarly, retrospective studies examining the ability of the PT or INR to predict hemorrhage at the time of invasive procedures have failed to show a correlation between the INR and hemorrhagic outcomes. Perioperative bleeding has been correlated with surgical inexperience with the procedure.

TABLE 2: Coagulation parameters in 30 plasma samples

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD (range)</th>
<th>Median</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (sec)</td>
<td>13.8 (12.8–17.6)</td>
<td>13.6</td>
<td>9–12.5</td>
</tr>
<tr>
<td>INR</td>
<td>1.39 (1.3–1.7)</td>
<td>1.35</td>
<td>0.9–1.2</td>
</tr>
<tr>
<td>PTT (sec)</td>
<td>28.6 (19.3–33.7)</td>
<td>29.0</td>
<td>24.5–34.5</td>
</tr>
<tr>
<td>factor II (%)</td>
<td>73 (40–107)</td>
<td>72</td>
<td>77–128</td>
</tr>
<tr>
<td>factor VII (%)</td>
<td>64 (25–124)</td>
<td>57</td>
<td>62–148</td>
</tr>
<tr>
<td>factor VIII (%)</td>
<td>121 (43–547)</td>
<td>118</td>
<td>50–150</td>
</tr>
</tbody>
</table>

In fact, the patients who received plasma therapy to correct the INR had significant delays (mean 19.2 hours) in ICP monitor placement as compared with those who did not get plasma (mean 8.8 hours, p < 0.002). Furthermore, not all patients with a moderately prolonged INR (> 1.7) had complete correction after receiving several units of plasma, and ICP monitors were placed with INRs > 1.3 in these patients. The study did not show an increase in the bleeding complication rates in patients with an INR of 1.3–1.6 with or without plasma, and the authors concluded that the data did not support plasma therapy for an INR ≤ 1.6.

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TABLE 3: Values of PT, INR, and PTT at 2 different time periods

<table>
<thead>
<tr>
<th>Study Period</th>
<th>No. of Transfusion Requests (no. of patients)</th>
<th>Procedure Performed (no. of patients)</th>
<th>Time of Testing</th>
<th>PT (sec)</th>
<th>INR</th>
<th>PTT (sec)</th>
</tr>
</thead>
<tbody>
<tr>
<td>before change in</td>
<td>99 (69)</td>
<td>68 transfusions (46)</td>
<td>at request</td>
<td>13.42</td>
<td>1.30</td>
<td>28.9</td>
</tr>
<tr>
<td>guidelines</td>
<td></td>
<td></td>
<td>in 24 hrs</td>
<td>12.10</td>
<td>1.18</td>
<td>28.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>31 nontransfusions (29)</td>
<td>at request</td>
<td>11.90</td>
<td>1.16</td>
<td>27.65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in 24 hrs</td>
<td>11.29</td>
<td>1.10</td>
<td>27.43</td>
</tr>
<tr>
<td>after change in</td>
<td>15 (14)</td>
<td>2 transfusions (2)</td>
<td>at request</td>
<td>14.10</td>
<td>1.40</td>
<td>26.60</td>
</tr>
<tr>
<td>guidelines</td>
<td></td>
<td></td>
<td>in 24 hrs</td>
<td>12.8</td>
<td>1.30</td>
<td>27.10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13 nontransfusions (12)</td>
<td>at request</td>
<td>12.22</td>
<td>1.18</td>
<td>27.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in 24 hrs</td>
<td>11.54</td>
<td>1.14</td>
<td>26.99</td>
</tr>
</tbody>
</table>

Conclusions

In summary, our data showed that patients with mildly elevated INR (≤ 1.7) have hemostatically normal levels of important coagulation factors. This revelation led to a > 75% reduction in plasma therapy for such patients at our institution. Therefore, we recommend that plasma should not be transfused to neurosurgical patients to simply correct mild elevations in PT/INR.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following: Conception and design: Sarode, Madden, Rutherford. Acquisition of data: Sarode, Matevosyan, Madden, Barnett. Analysis and interpretation of data: Sarode, Matevosyan, Beshay. Drafting the article: Sarode, Matevosyan, Beshay. Critically revising the article: Sarode, Madden, Barnett, Beshay, Rutherford. Review of final version of the manuscript and approved it for submission: all authors. Statistical analysis: Sarode, Matevosyan. Administrative/technical/material support: Sarode. Study supervision: Sarode, Matevosyan, Madden.

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