Retrospective analysis of bleeding events after central venous catheter placement in thrombotic thrombocytopenic purpura

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1. Introduction

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic disorder of the microvasculature and sometimes macrovasculature, caused by a severe deficiency (<10%) of ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif-13), an enzyme that cleaves von Willebrand factor and maintains normal multimer distribution in the plasma. It is a rare, serious condition with high mortality of 90%, if untreated [1]. Acquired TTP occurs due to an autoantibody against ADAMTS13, whereas congenital TTP is secondary to a genetic mutation in the ADAMTS13 gene. A severe deficiency of ADAMTS13 activity distinguishes TTP from other thrombotic microangiopathies (TMAs), and the utility of ADAMTS13 to guide therapy decisions is well-established [1-4].

The standard treatment includes emergent therapeutic plasma exchange (TPE), for which a central venous catheter (CVC) is often required. The platelet count in TTP is usually <30x10^9/L due to consumption in microthrombi. Platelet transfusion is a relative contraindication and is reserved for intracranial hemorrhage [2]. The practice of transfusing platelets prior to a CVC placement to prevent bleeding is controversial because TTP is a thrombotic condition, and platelet transfusion may be detrimental, serving as adding “fuel to the fire” phenomenon [2]. Goel et al. found that platelet transfusions in 10,624 hospitalizations for TTP were associated with higher odds of arterial thrombosis, acute myocardial infarction, and mortality than those who were not transfused [2].

Our local protocol considers platelet transfusion to be absolutely contraindicated in TTP patients. Therefore, we retrospectively analyzed TTP patients who presented with acute episodes to two institutions over nine years for clinically significant bleeding complications.
2. Material and Methods

2.1 Study Design

We performed a retrospective analysis of patients with TTP admitted to Parkland Health and Hospital Systems and University Hospitals at the University of Texas Southwestern Medical Center. An ADAMTS13 activity <10% confirmed the diagnosis of TTP. The selected laboratory parameters, including platelet counts, hemoglobin values, and episodes of thrombotic or bleeding complications, were analyzed. The local Institutional Review Board approved the study.

2.2 Study Population

Patients admitted to two hospitals from January 1, 2005, to October 1, 2018, with suspected TMA (thrombotic microangiopathy) and severe ADAMTS13 deficiency (<10%) prior to TPE, were included. Suspected TMA was defined as when the patients presented with unexplained thrombotic microangiopathy with thrombocytopenia (platelet count <100 x 10⁹/L), presence of peripheral smear schistocytes, and elevated lactic dehydrogenase (LDH).

Subjects not fulfilling the inclusion criteria described above were excluded. The following subjects were also excluded: 1) subjects who, upon chart review were retrospectively deemed unlikely to have had a TMA at the time of ADAMTS13 testing (documented alternative discharge diagnosis) and subjects transferred from another hospital where plasma exchange had already been performed.

2.3 Data collected

The patient information collected included the following: age and sex, clinical presentation, platelet count, hemoglobin/hematocrit, and cardiac enzymes, ADAMTS13 activity, and inhibitor level. Relevant management information was also collected, including TPE, sites of central venous catheters, bleeding or thrombotic episodes, platelet and blood transfusion.
2.4 Statistical analysis

All statistical analyses were performed with Stata software, version 15 (College Station, TX: Stata Corp LLC). Data were analyzed for central tendency and dispersion measures for patients with TTP. The statistical significance of the difference in these measures between cohorts was determined with a threshold of \( p < 0.05 \). In Table 1, means are listed with standard deviation in parentheses, and percentages listed with frequency in parentheses.

3. Results

3.1 Baseline characteristics

We identified 95 acute episodes of TTP (ADAMTS13 <10%) from September 1, 2009, to October 1, 2018; 26 episodes were excluded for insufficient documentation or no CVC placement. The charts of 61 remaining patients (69 episodes) were reviewed for relevant clinical and laboratory data.

Table 1 displays the baseline characteristics of the patients, along with patients with and without bleeding episodes. The mean and median platelet counts were \( 35 \times 10^9/L \) and \( 14 \times 10^9/L \), respectively. One patient received a single unit of platelet transfusion due to suspected HELLP syndrome before TTP diagnosis.

3.2 Bleeding Complications

Of 69 TTP episodes, nine (13%) had bleeding after a CVC placement. Seven were minor bleeds; five had hematomas at the insertion site (three femoral, two internal jugular, IJ), and two had oozing from the catheter sites (both right femoral). There were two major bleeds following the femoral CVC placement (one was a brisk bleed from requiring transfusions for an accidental femoral arterial puncture, and the other was a persistent bleed from the right femoral catheter after pressure was applied, also possibly an arterial placement). Both patients were classified as
obese. In the first patient with a major bleed, the platelet count was 13 x 10^9/L, requiring three units of blood transfusions after the line placement. The second such patient with a platelet count of 8 x 10^9/L developed hemorrhagic shock with hypotension after the catheter was removed (possibly suspected arterial bleed) and was transfused with four units of blood. A femoral compression device was applied to this patient. None of them required any platelet transfusion for arterial bleeding complications.

The median platelet count prior to the line placement among those bled was 12 x 10^9/L (range 3-44) compared to those who did not bleed, which was 15 x 10^9/L (range 4-257, p=0.258). Among the 44 episodes with a platelet count <20 x 10^9/L, 7 (16%) had bled. Among the nine cases where patients bled, 7 had femoral CVC placed, and 2 had internal jugular CVCs. Among the 60 episodes of CVC placement with no bleed, 63% had femoral lines, and 37% had internal jugular lines.

3.3 Thrombotic complications

There were three thrombotic episodes, including a right IJ permacath line thrombus with pulmonary embolism on day 27, a non-ST elevation myocardial infarction on day 7, and a right IJ thrombosis on day 5 of hospital admission. None of these patients received platelet transfusions during their hospital stay.

4. Discussion

Our retrospective analysis of bleeding complications following the line placement showed that the major bleeding was uncommon, and the median platelet count was similar in patients who bled (12 x 10^9/L) versus those who did not (15 x 10^9/L). There were seven minor and two major bleeds, with the latter seemingly related to technical challenges during the femoral line placement including the body habitus. These findings suggest that platelet
transfusion is unnecessary before line placement in TTP and should be avoided given the risk of arterial thrombotic complications, as described by Goel et al. [2]. Furthermore, the preference for femoral access is likely due to a combination of factors, including technical ease and relative ease of bleeding control by pressure compared to the other sites. The electronic medical records do not provide information when the supervising physician had to assist a resident physician during the placement.

The existing literature largely supports the avoidance of platelet transfusion before CVC placement in TTP, except in the case of a life-threatening bleed. Notably, Goel et al. analyzed 10,624 TTP hospitalizations, calculating an odds ratio of 5.8 for arterial thrombosis after receiving platelet transfusion when comparing TTP to immune thrombocytopenic purpura admissions [2]. Another investigation of 8,203 TTP hospitalizations reports a 2.2 odds ratio for mortality in TTP patients who received platelet transfusions [3]. A few other smaller studies also conclude that platelet transfusions before CVC placement is unnecessary based on minimal blood loss during the procedure and the lack of major bleeding complications [2,4]. A case report describes two TTP patients who developed arterial thromboses after prophylactic platelet transfusion before CVC insertion; one developed neurologic complications within hours of transfusion, and the other had a fatal myocardial infarction within an hour [5].

A retrospective review of 54 TTP patients from the Oklahoma registry reported platelet transfusions in 33 and no platelet transfusion in 21 patients [6]. The mean platelet count in the two groups was similar ($11 \times 10^9$/L). There was no post-transfusion count reported to show significant increment. They reported higher severe neurological adverse outcomes in 52% of patients who were transfused as compared to 33% in those who were not transfused platelets ($p=0.190$). The bleeding complications were rare with one in both groups. Thus, there does not
seem to be any benefit of prophylactic platelet transfusion for CVC placement in TTP patients; rather, there was a trend of higher neurological adverse outcomes in those who were transfused. Several retrospective studies have suggested that it is the experience of the proceduralist and the techniques used (landmark-based versus ultrasound-guided) for CVC placement that is associated with bleeding risk rather than the platelet count [7-9]. The frequent use of ultrasound-guided line placement has significantly reduced the number of attempts needed to place the line, arterial punctures, and major bleeding [10].

Our study has all the limitations of any retrospective analysis, and a larger sample size is needed to assess patient outcomes, particularly concerning thrombotic complications post-transfusion. A previous study also sought to investigate if a platelet transfusion is necessary before line placement in TTP patients and only had a sample of 11 patients identified to have TTP [11]. However, with the general understanding of TTP’s pathophysiology, it is unlikely that a randomized clinical trial for platelet transfusion versus no transfusion is necessary or feasible.

5. Conclusions

In conclusion, it appears that the major bleeds in TTP patients are probably due to technical challenges that are unrelated to the platelet count. With the introduction of ultrasound-guided techniques, the incidence of rare major bleeds is likely to be reduced. In the absence of convincing evidence to the contrary, platelets should not be prophylactically transfused to reduce the presumed risk of bleeding during CVC placement in patients suspected of TTP.

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References


Table 1. Baseline characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>TTP Group (N=69 episodes)</th>
<th>Bleeding group (N=9 episodes)</th>
<th>Non-bleeding group (N=60 episodes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>47.73 (15.4)</td>
<td>49.9 (19.9)</td>
<td>47.31 (14.6)</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>31.9% (22)</td>
<td>33.3% (3)</td>
<td>31.7% (19)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>50.7% (35)</td>
<td>55.6% (5)</td>
<td>50.0% (30)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>15.9% (11)</td>
<td>22.2% (2)</td>
<td>15.0% (9)</td>
</tr>
<tr>
<td>Asian</td>
<td>4.3% (3)</td>
<td>0.0% (0)</td>
<td>5.0% (3)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>5.8% (4)</td>
<td>22.2% (2)</td>
<td>3.3% (2)</td>
</tr>
<tr>
<td>Median baseline platelet count (x 10^9/L)</td>
<td>14 (55.4)</td>
<td>12 (13.9)</td>
<td>15 (59.2)*</td>
</tr>
<tr>
<td>Platelet transfusion performed</td>
<td>1.4% (1)</td>
<td>0.0% (0)</td>
<td>1.7% (1)**</td>
</tr>
<tr>
<td>Site of central line</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right IJ</td>
<td>31.9% (22)</td>
<td>11.1% (1)</td>
<td>35.0% (21)</td>
</tr>
<tr>
<td>Left IJ</td>
<td>4.3% (3)</td>
<td>11.1% (1)</td>
<td>3.3% (2)</td>
</tr>
<tr>
<td>Right femoral</td>
<td>46.4% (32)</td>
<td>55.6% (5)</td>
<td>45.0% (27)</td>
</tr>
<tr>
<td>Left femoral</td>
<td>17.4% (12)</td>
<td>22.2% (2)</td>
<td>16.7% (10)</td>
</tr>
</tbody>
</table>

TTP= Thrombotic thrombocytopenic purpura. * p = 0.258, ** = received platelet transfusion for suspected diagnosis of HELLP syndrome
ABSTRACT

Background: Thrombotic thrombocytopenic purpura (TTP) is a thrombotic disorder caused by severe deficiency of ADAMTS13. Platelets are transfused prophylactically in non-TTP patients for central venous catheter (CVC) with a count <20x10⁹/L to prevent bleeding. However, transfusing platelets in TTP prior to CVC placement remains controversial due to concern for arterial thrombosis and mortality. At our center, platelet transfusion is contraindicated in TTP, therefore, we analyzed data for bleeding complications following CVC placement.

Study Design and Methods: 95 acute episodes of TTP were identified. Twenty-six episodes were excluded for insufficient documentation or no CVC placement. The charts of 69 remaining episodes were reviewed.

Results: Of 69 TTP episodes, nine (13%) had bleeding after a CVC placement. Of these, seven bleeds were minor, and the two were major related to the technical issues during femoral venous access causing arterial bleeds. Median platelet count before the CVC placement among those experiencing bleeding complications was 12 x 10⁹/L (range 3-44) as compared to median count of 15 x 10⁹/L (range 4-257) in those who did not bleed (p=0.258). Among 44 episodes with a platelet count <20 x 10⁹/L, seven (16%) had bleeds.

Conclusion: Major bleeding complications following CVC placement in TTP is uncommon and most likely related to technical challenges. Median platelet count was similar in patients who bled versus those who did not, suggesting that platelet transfusion is unnecessary to correct platelet count prior to a CVC placement in TTP.

Keywords: Thrombotic thrombocytopenic purpura (TTP), bleeding, central venous catheter, platelets, prophylactic transfusions