Safety of Tissue Plasminogen Activator for Acute Stroke in Menstruating Women

Theodore H. Wein, MD, FRCPC; Susan L. Hickenbottom, MD; Lewis B. Morgenstern, MD; Andrew M. Demchuk, MD, FRCPC; James C. Grotta, MD

Background—Menses is a theoretical contraindication to intravenous tissue plasminogen activator (tPA) treatment. We sought to establish the safety of intravenous tPA in the treatment of acute ischemic stroke in women who are actively menstruating.

Summary of Report—We provide a case report and review of the National Institute of Neurological Disorders and Stroke (NINDS) database for women coded as actively menstruating. Nine subjects were coded as actively menstruating in the NINDS trial (4 placebo and 5 in the treatment). One subject in the treatment group who had a 1-year history of dysfunctional uterine bleeding required emergent uterine artery ligation. We also report a case of a woman requiring transfusion after intravenous tPA administration for acute ischemic stroke.

Conclusions—Intravenous tPA may be administered relatively safely in women who are menstruating and should be used with caution in women with a history of dysfunctional uterine bleeding. Potential patients should be advised that they might require transfusion for increased menstrual flow. (Stroke. 2002;33:2506-2508.)

Key Words: hemorrhage □ menstrual cycle □ menstruation □ stroke □ tissue plasminogen activator □ women

Outside of pregnancy, there are currently no specific sex-related contraindications for the use of tissue plasminogen activator (tPA) in the treatment of acute stroke. Currently, active bleeding, internal bleeding, and bleeding at a noncompressible site are considered relative contraindications to the use of tPA. This guideline raises the question of whether menstruating women with acute strokes should be excluded from receiving thrombolytic therapy. There is little literature regarding the safety of thrombolysis during menstruation, and those cases reported are confined to cardiac and peripheral vascular disease, in which case most patients have received thrombolics in conjunction with anticoagulants.1-9

Of the 25 cases reported to date, only 2 have required transfusion, and no serious sequelae have occurred.

In this communication, we report our experience with a menstruating woman treated with tPA for acute ischemic stroke. In addition, we report the effects of thrombolytic therapy in women who were menstruating when they were enrolled in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study.10

Subjects and Methods

Case Report

A 46-year-old woman presented to the emergency department 60 minutes after the onset of dysphasia, dysarthria, and a right hemiparesis. Her National Institutes of Health Stroke Scale (NIHSS) score was 10. Past medical history was significant for a 25-pack-year history of smoking and oral contraceptive use. There was no history of hypermenorrhea or dysfunctional uterine bleeding. She was within the first 20 hours of her menses. She met all published criteria for eligibility for thrombolytic therapy. After discussion of potential risks and benefits with the patient, intravenous tPA was administered per the NINDS protocol with treatment beginning at 100 minutes from onset of symptoms. Initial blood pressure was 140/82 mm Hg, with a baseline hemoglobin of 10 g/dL (normal, 12 to 16 g/dL) and hematocrit of 31.8% (normal, 37% to 42%), with a normal platelet count as well as prothrombin time and partial thromboplastin time.

After 25 minutes of tPA infusion, there was a marked increase in menstrual flow, which required 5 sterile pads within 2 hours. Blood pressure decreased to 90/40 mm Hg and did not respond to intravenous fluids. Four hours from the onset of hypotension, her hemoglobin and hematocrit levels had dropped to 8 g/dL and 23%, respectively. Because of her poor response to intravenous fluids and continued heavy flow, she was transfused with 2 U of packed red blood cells. Normal menstrual flow resumed 12 hours after initiation of therapy or approximately 30 hours into her menses. A cerebral arteriogram revealed an occluded M1 segment of the left middle cerebral artery, and MRI of the brain revealed hemorrhagic insults to the left caudate as well as a cortical/subcortical parietal infarct. Transesophageal echocardiography and a hypercoagulable workup were unrevealing. Her 3-week NIHSS score was 5.

The methods, inclusion criteria, and results of the NINDS tPA stroke trial have been described previously.10 Menstruation was not an exclusion criterion for the study, and the case report form captured whether a subject was menstruating at the time of enrollment. We explored the NINDS database and identified all subjects who were coded as menstruating at the time of enrollment. We then
explored all adverse events associated with each of these subjects, particularly looking for hypotension, increased bleeding, need for transfusion, use of vasopressive agents, and emergent surgery. NIHSS score and hematocrit level at baseline and 24 hours were analyzed.

A MEDLINE and PUBMED search was performed in November 2001 (key search words: tPA, thrombolysis, menses, menstruation, hemorrhage) to identify all other cases in the medical literature. Genentech (San Francisco, Calif) was also contacted to review their files for other cases of tPA being used in menstruating women. All Genentech cases had been detected in the MEDLINE/PUBMED searches.

Results

In the NINDS database, 9 women (4 in the placebo group, 5 in the treatment group) were found to be menstruating on the case report form (Table 1). Of the 5 patients who received tPA, only case 2 experienced any adverse effects. This patient had a 1-year history of dysfunctional vaginal bleeding. tPA infusion was discontinued 20 minutes into infusion secondary to persistent vaginal bleeding, tachycardia, mild hypotension, and oozing from the gums. She was found to have a decreased fibrinogen level and a hematocrit of 26 and was treated with 3 units of packed red blood cells. Seventy-two hours after her event, she underwent a previously scheduled elective uterine artery embolization. She was initially suspected to have a uterine mass, but subsequent investigations were negative. No significant alterations in menstrual flow were reported among any of the other tPA-treated subjects. Case 4 was also reported to be menstruating; however, this case could not be independently confirmed on review of the case report form and clinical notes. She was noted to be 60 years of age and presented at baseline with gross hematuria, but vaginal bleeding could not be independently confirmed. A drop in hematocrit from 41.9% to 41% was noted; however, no hypotension or adverse sequelae were noted. One patient in the placebo group experienced slightly increased menstrual flow (case 9).

Table 2 summarizes the PUBMED/MEDLINE searches of all cases reported in the literature of women who were menstruating and received thrombolysis. There are no case reports of women receiving thrombolytic agents for acute stroke. In total, 25 women were identified who had received either tPA and/or streptokinase for either acute myocardial infarction or deep vein thrombosis. Only in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-1) trial4 were 2 of 12 women with acute myocardial reported to have in-

### Table 1. Summary of Actively Menstruating Women in the NINDS tPA Trial (n=624: tPA=312/Placebo=312)

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, y</th>
<th>tPA/Placebo</th>
<th>Baseline Hematocrit, %</th>
<th>24-h Hematocrit, %</th>
<th>Baseline NIHSS</th>
<th>24-h NIHSS</th>
<th>Hypotension/Vasopressors</th>
<th>Increased Menstrual Flow</th>
<th>Transfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>tPA</td>
<td>42.6</td>
<td>34.3</td>
<td>26</td>
<td>8</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>tPA</td>
<td>33.4</td>
<td>29.7</td>
<td>5</td>
<td>0</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
<td>tPA</td>
<td>30.1</td>
<td>26.9</td>
<td>5</td>
<td>0</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>60</td>
<td>tPA</td>
<td>41.9</td>
<td>41</td>
<td>17</td>
<td>17</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>tPA</td>
<td>40.6</td>
<td>37.7</td>
<td>17</td>
<td>4</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>34</td>
<td>Placebo</td>
<td>35.8</td>
<td>34.3</td>
<td>6</td>
<td>3</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>41</td>
<td>Placebo</td>
<td>42.7</td>
<td>37.7</td>
<td>16</td>
<td>9</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
<td>Placebo</td>
<td>47</td>
<td>46</td>
<td>8</td>
<td>3</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>Placebo</td>
<td>33.5</td>
<td>36.1</td>
<td>28</td>
<td>22</td>
<td>No</td>
<td>Slight</td>
<td>No</td>
</tr>
</tbody>
</table>

### Table 2. Literature Review of All Reported Cases of Thrombolytic Therapy in Actively Menstruating Women

<table>
<thead>
<tr>
<th>Authors</th>
<th>n/Thrombolytic Agent</th>
<th>Indication</th>
<th>Alteration in Menstrual Flow</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chop et al1</td>
<td>1/tPA</td>
<td>MI</td>
<td>Slightly increased</td>
<td>Mild anemia on day 5; no transfusion</td>
</tr>
<tr>
<td>Conti2</td>
<td>1/urokinase</td>
<td>MI</td>
<td>No</td>
<td>No transfusion</td>
</tr>
<tr>
<td>de Gregorio et al3</td>
<td>1/streptokinase</td>
<td>MI</td>
<td>No</td>
<td>No transfusion</td>
</tr>
<tr>
<td>Karnash et al4</td>
<td>12/tPA and/or streptokinase</td>
<td>MI</td>
<td>2/12 moderate increase</td>
<td>2 transfusions</td>
</tr>
<tr>
<td>Lanter et al4</td>
<td>5/tPA</td>
<td>MI</td>
<td>No</td>
<td>No transfusion</td>
</tr>
<tr>
<td>Lee and Garza4</td>
<td>1/tPA</td>
<td>MI</td>
<td>No</td>
<td>No transfusion</td>
</tr>
<tr>
<td>McCallister et al7</td>
<td>1/tPA</td>
<td>MI</td>
<td>Slightly decreased</td>
<td>No transfusion</td>
</tr>
<tr>
<td>Sekyema and Baltazar8</td>
<td>1/tPA</td>
<td>MI</td>
<td>No</td>
<td>No transfusion</td>
</tr>
<tr>
<td>Simel et al8</td>
<td>1/streptokinase</td>
<td>MI</td>
<td>Slightly decreased</td>
<td>No transfusion</td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; DVT, deep vein thrombosis.
creased menstrual flow requiring transfusion. It is not specified to which arm of the trial they were randomized (streptokinase with subcutaneous heparin, streptokinase with intravenous heparin, accelerated tPA with intravenous heparin, or combination tPA with streptokinase with intravenous heparin). There is 1 case report of streptokinase being used to treat a deep vein thrombosis and 2 cases of tPA being used for acute myocardial infarction in which slightly increased menstrual flow was noted, but no reported hemodynamic compromise was noted, nor was there a need for transfusion.

Discussion

Hemostasis is maintained in the majority of tissues by adhesion and activation of platelets, which leads to platelet aggregation followed by activation of the clotting cascade and deposition of fibrinogen. Menstruation, in contrast, is regulated not only by platelet plugs and fibrin but also by prostaglandins, hormones, and myometrial contraction.11 Menstruation is a result of progestosterone withdrawal. As progestosterone levels decrease, the superficial endometrium begins to invaginate, leading to the development of fissures and subsequent bleeding. Subsequently, the endometrium begins to desquamate. As the endometrium begins to thin, the spiral arteries (the main arterial suppliers to the endometrium) begin to coil as a result of both direct hormonal influences and the lack of a need to be fully extended to supply the superficial endometrium, which is now thinning and desquamating. As the arteries coil, they begin to leak, resulting in the initial menstrual flow. During the first 0 to 20 hours of menstruation, hemostasis is maintained predominantly by platelet plugs and fibrin. Hemostasis after the initial 20 hours of menstruation is maintained by constriction of the spiral arterioles in the basal layers of the endometrium, myometrial contraction, and tissue regeneration and is not dependent on clot formation. Clot formation does not occur as the endometrium releases plasminogen activators.

The increased menstrual flow in our case report that subsequently required transfusion is most likely due to the fact that the subject was in the first 20 hours of her menses, during which hemostasis is regulated predominantly, but not exclusively, by platelet plugs and fibrinogen. Despite the increased menstrual flow and need for transfusion, she had a good outcome, and her NIHSS score decreased by 5 points at the end of 3 weeks.

In the NINDS database, the only subject with an adverse event had a 1-year history of continuous vaginal bleeding. It should be noted that this case does not represent menstruation but dysfunctional uterine bleeding. Hemostatic control was obtained after cessation of tPA and transfusion. This subject was found to have a low fibrinogen and had bleeding at multiple sites.

This case series is the first report regarding the safety of intravenous tPA in menstruating women for acute ischemic stroke and is the second largest series of thrombolytic use in menstruating women. On the basis of our data and review of the limited literature and the physiology of hemostasis during menstruation, we conclude that thrombolytic therapy may be administered relatively safely in women who are menstruating and should not be withheld or delayed. However, patients should be advised that they may have an increased rate of menstrual flow and may require transfusion, especially if treatment is necessary during the first day of menses. In individuals with dysfunctional uterine bleeding, which may be more frequent in stroke-aged women, thrombolytics should be used with caution because hemostatic control normally present during menstruation is not applicable to this circumstance. In such cases with dysfunctional uterine bleeding, emergent consultation with the gynecology department should be obtained, and the risk and benefits of using a thrombolytic agent should be analyzed carefully before treatment.

Acknowledgments

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References

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