Thromboelastography for the Prediction of Bleeding After Transplant Renal Biopsy

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ABSTRACT

The ability of prebiopsy coagulation assays to predict mild postbiopsy bleeding was evaluated in renal transplant patients undergoing renal allograft biopsy (N = 120). The coagulation assays studied included the bleeding time, prothrombin time, partial thromboplastin time, platelet count, and thromboelastograph (TEG). Coagulation results were defined as abnormal if they fell outside the established normal reference range. Bleeding was defined as a drop in the hematocrit equal to or more than 4 points 6 h after the procedure or ultrasound evidence of a new perirenal hematoma. Overall, 21% of patients showed evidence of mild bleeding. Of those who bled, 78% had normal results on all coagulation tests, indicating that most mild bleeding was not associated with coagulation abnormalities. Of the assays tested, only abnormal TEG:angle (P < 0.01) and TEG:k (P < 0.04) values were associated with an increased risk of bleeding. Bleeding times were not predictive of an increased risk of postbiopsy bleeding; five patients had abnormal bleeding times ranging from 10 to 20 min of whom only one bled. All prothrombin time, partial thromboplastin time, and platelet count abnormalities were mild (e.g., no prothrombin times longer than 15 s, no platelet counts below 129,000/μL); none of these assays predicted postbiopsy bleeding. Other clinical characteristics, including patient age, sex, serum creatinine, blood pressure (if less than 160/90 mm Hg), number of biopsy passes, or renal pathology, did not appear to influence bleeding after biopsy. It was concluded that most bleeding after transplant renal biopsy was not associated with coagulation abnormalities and that the TEG was the best assay for detecting mild coagulation abnormalities associated with an increased risk of bleeding.

Bleeding after renal biopsy has been linked to biopsy technique, hypertension, renal pathology, and coagulation abnormalities (1-9). Hemostatic screening before biopsy is intended to detect those who have significant abnormalities before the procedure so appropriate therapy can be given to prevent bleeding. Prebiopsy evaluation designed to limit the risk of bleeding has often included a prothrombin time (PT), partial thromboplastin time (PTT), platelet count, and bleeding time (BT) (6,8,10). Recent studies, however, have questioned the utility of the BT; it is invasive and subject to performance variability, and the predictive value for bleeding in individual patients at sites other than the skin has been poor (11,12). In an effort to determine if the prebiopsy evaluation could be safely simplified, we compared the thromboelastograph (TEG) with more common hemostatic tests as predictors of bleeding after transplant renal biopsy.

The TEG was chosen for examination in this study because it produces an overall evaluation of the coagulation, platelet, and fibrinolytic systems in one assay. The TEG measures the strength and shear elasticity of a clot as it forms, matures, and lyases. The TEG has proved to be more useful than the BT, PT, and PTT for predicting bleeding after cardiac bypass surgery and liver transplantation (13-16). In addition, it is easy to interpret. The output from the TEG is a graph (Figure 1). The width of the graph at any point is the clot strength or elasticity. Five graph parameters are measured when the TEG is complete. The "r" value is a measure of the time it takes for clotting to begin; it is similar to a whole-blood clotting time. If the "r" value is prolonged, it indicates a possible coagulation deficiency that could be further investigated with PT, PTT, and factor assays. The "k" value and angle (α°) indicate how fast clot strength is increasing once clotting starts. Reduced "k" or angle may be due to any combination of coagulation deficiencies, reduced platelet function, and reduced platelet count. The maximum amplitude (MA) or maximum width of the graph is an indication of the maximum attainable clot strength. Decreases in MA are associated with reduced platelet function or number and with reduced fibrinogen levels. The amplitude after 60 minutes (A60) is a measure of fibrinolysis; if the A60 is significantly less than the MA, it indicates that in vivo clot lysis may be occurring.

Simple inspection of the graph provides the majority of the information. A normal graph similar to that shown in Figure 1 shows a rapid onset of clotting, with a sufficient width and no evidence of lysis, indicating no abnormalities of the coagulation, platelet, or fi-
NORMAL
Thromboelastograph

ABNORMAL
Thromboelastograph

Figure 1. TEG tracing. The width or amplitude of the tracing at any point is proportional to the clot shear modulus (elastic strength). Five parameters are measured on the curve: (1) the r value is the time to the start of clot onset, similar to a whole-blood clotting time; (2) the k value is the time from the start of clotting to an amplitude of 20 mm; (3) the angle (α°) is measured from the center line to a line drawn from the start of clotting tangential to the clotting curve. Both the "k" and the angle provide an indication of the rate of clot formation; (4) the MA is a measure of maximum clot strength; and (5) the A60 is compared with the MA, if significantly reduced, it indicates that fibrinolysis is occurring. This diagram shows a normal TEG with a rapid clot onset (short "r"), rapid clot formation (short "k" and large angle), normal amplitude, and no change in A60.

brinolytic systems. An abnormal graph (Figure 2) with a prolonged onset time, a narrow width, or a reduction in width at the end indicates abnormal clotting and suggests the need of further hemostasis workup. In order to determine which coagulation measurements and intrabiopsy factors predict bleeding after renal biopsy, a prospective study was undertaken comparing standard coagulation tests, TEG, biopsy technique, and renal pathology with the incidence of bleeding in patients undergoing renal biopsy on transplanted kidneys.

METHODS

Patient Population

All patients undergoing transplant (N = 120) renal biopsy by nephrologists in training under the direction of one attending nephrologist from May 1993 through May 1994 were prospectively studied. None of the patients had a history of bleeding during or after surgery or dental procedures. One patient treated with fresh frozen plasma before biopsy was eliminated from the study. None of the patients were being treated with heparin or nonsteroidal anti-inflammatory medications; however, 98 of 120 patients were receiving aspirin, 325 mg once per week.

Biopsy Procedure

Patients were not biopsied if they had a blood pressure of more than 160/100 mm Hg. All biopsies were performed with a 16-gauge spring-loaded Temno (Bauer; Clearwater, FL) needle under real-time ultrasound guidance with local anesthesia and without the administration of intravenous fluids. Patients undergoing combined kidney and pancreas allograft biopsy received less than 500 mL of intravenous normal saline during the procedure.

Patients were observed for 6 h after the procedure. After the biopsy, the blood pressure was kept at less than 160/90 mm Hg. The hematocrit was checked 6 h after the biopsy.

Bleeding Endpoint

A drop in hematocrit equal to or more than 4 points 6 h after biopsy or ultrasound evidence of a new periureal hematoma was considered indicative of significant small postbiopsy hemorrhage. A drop in the hematocrit of equal to or more than 6 points was considered indicative of moderate hemorrhage. Blood transfusion requirements were also recorded.
Predictors of bleeding

The following potential predictors of bleeding were prospectively evaluated: age, sex, aspirin use (325 mg once per week as part of a transplant protocol), number of days between the last aspirin and biopsy, serum creatinine, pre-biopsy systolic blood and diastolic blood pressure, number of passes with the biopsy needle, physician performing the biopsy, ultrasonographer, presence of predominantly medullary tissue or vascular sclerosis on histopathologic examination of the biopsy sample, PT, PTT, platelet count, TEG, and BT.

Coagulation Assays

Blood for coagulation assays was anticoagulated by the addition of 4.5 mL of whole blood to 0.5 mL of 130 mmol/L sodium citrate. PT, PTT, and fibrinogen were measured in citrated plasma as previously described (17,18). TEG measurements were performed as previously described (19). Briefly, whole citrated blood samples were recalcified by the addition of 250 µL of whole citrated blood to 100 µL of prewarmed 0.645 g/dL calcium chloride. After 1 h, five measurements are made on the TEG tracing: the r value, the k value, the angle, the MA, and the A60 (Figure 1). Platelet counts were performed in EDTA-anticoagulated blood with an Abbott Cell Dyn 3000 flow-cytometric cell counter (Abbott Laboratories, Santa Clara, CA). Bleeding times were determined by use of the Simplate II method. (Organon Teknika, Durham, NC).

Statistical Analysis

Test results were defined as abnormal if they fell outside the established reference range (Table 1). The χ² test was used to determine whether abnormal test results were associated with an increased risk of bleeding. The χ² test was also used to determine whether other discrete variables (e.g., sex, aspirin use, vascular sclerosis) were associated with an increased risk of bleeding.

RESULTS

After renal biopsy, 27% of the patients met one of the criteria for small but significant bleeding. A hematocrit drop of at least 4 points was noted in 30, whereas 2 demonstrated ultrasound evidence of a hematoma immediately after biopsy. Five percent (6 of 120) dropped their hematocrit by 6 or more points, indicating moderate bleeding. No transfusions were given to any of the patients. In patients with mild and moderate bleeding after biopsy, 78 and 83%, respectively, had normal coagulation results on all assays. Thus, the majority of patients showing mild to moderate bleeding after renal biopsy did not have coagulation abnormalities, on the basis of the assays used in this study.

Overall, 21% of the transplant patients had at least one coagulation test (PT, PTT, BT, PLT, or any TEG value) outside the normal reference range. Having any test outside the reference range was not associated with an increased risk of bleeding. Table 1 shows the expected normal reference range, the percentage of patients with abnormal results, the range of abnormal results, and the statistical association between an abnormal result and bleeding. The only results that were significantly associated with bleeding were abnormal TEG:angle (α²) and TEG:k. Abnormal PT, PTT, BT, PLT, TEG:r, TEG:MA, and TEG:A60 results were not associated with bleeding. TEG:angle and TEG:k parameters measure the rate of clot formation once clotting has begun. TEG:angle and TEG:k results are a combination of coagulation function, platelet function, and platelet count. In contrast, the TEG:r, PT, and PTT measure the time to the onset of clotting, not the formation of the clot itself. The other assay in theory able to detect platelet function defects was the BT.

BT were not associated with an increased risk of postbiopsy bleeding; five patients had abnormal bleeding times ranging from 10 to 20 min, of whom only one bled. In reviewing Table 1, it should be noted that the majority of PT, PTT, and platelet count abnormalities were mild. None of the transplant patients

| Test | Normal Reference Range | No. Bleeding | Range of Abnormal Results | No. Bleeding | χ² Test<br> |<sup>a</sup> |
|------|------------------------|-------------|---------------------------|-------------|---------|<sup>a</sup>| |
| TEG:angle (degrees) | 54–88 | 24 of 94 | 46–53 | 5 of 7 | <i>P < 0.01</i> |
| TEG:k (mm) | 2–7 | 26 of 97 | 8–9 | 3 of 4 | <i>P < 0.04</i> |
| TEG:r (mm) | 3–22 | 29 of 101 | NA<sup>b</sup> | NA | NS<sup>c</sup> |
| TEG:MA (mm) | 48–70 | 28 of 97 | 42–46 | 1 of 4 | NS | |
| TEG:A60 (mm) | 45–70 | 28 of 95 | 40–44 | 1 of 6 | NS | |
| PT (s) | 11–13.6 | 33 of 110 | 13.9–14.7 | 1 of 9 | NS | |
| PTT (s) | 24–36 | 34 of 118 | 37 | 0 of 2 | NS | |
| Platelet count (1,000/µL) | 150–400 | 33 of 117 | 129–148 | 1 of 3 | NS | |
| BT (min) | 1–9 | 28 of 100 | 10–20 | 1 of 5 | NS | |

<sup>a</sup>The number of patients bleeding with a normal result was compared with the number of patients bleeding with an abnormal result by use of the χ² test.

<sup>b</sup>NA, not applicable; all results were normal.

<sup>c</sup>NS, not significant; <i>P > 0.05</i>.
had a PT longer than 15 s, a PTT longer than 37 s, or a platelet count less than 129,000/μL.

The sensitivity, specificity, positive predictive value, and negative predictive value for TEG:angle, BT, and PT for small postbiopsy hemorrhage are shown in Table 2. The TEG:angle was the best in all categories; the worst was the PT. An abnormal TEG:angle had a positive predictive value of 71%, as compared with 20% for the BT and only 11% for the PT.

Patient age, sex, serum creatinine (bleeding was noted in 27% of patients with a creatinine of more than 2.0 mg/dL and 27% of those with a creatinine less than or equal to 2.0 mg/dL; P = 0.95), systolic or diastolic blood pressure in the ranges kept during and postbiopsy, the number of biopsy passes (median of four passes in those who bled and those who did not), the use and absence of aspirin administration, the identity of the ultrasonographer or nephrologist, or the presence of vascular sclerosis or predominantly medullary tissue (P = 0.098) were not associated with the risk of bleeding after renal biopsy.

**DISCUSSION**

Bleeding after renal biopsy has been reported to occur more frequently when: (1) large-bore needles are used; (2) needle penetration reaches the medulla; (3) radiologic guidance is not used; (4) renal tissue demonstrates fibrosis and nephrosclerosis; (5) the patient has hypertension; and (6) a coagulopathy is present (1-9,20-24). To prevent bleeding, hypertension is treated, needle sizes have decreased, biopsies are performed under ultrasound guidance, and biopsy in the presence of a coagulopathy is avoided by the performance of screening coagulation assays (8-10,25-27). However, the predictive value for procedural bleeding of mild abnormalities of the standard coagulation assays used (PT, PTT, platelet count, and BT) has been shown in the past and is shown in this study to be poor (11,12,28). The BT in particular is a poor prebiopsy screening test. Recent reviews have concluded that it should not be used for preoperative screening (11,12). The BT is prone to procedural problems, is affected by a number of medications associated with minimal bleeding risk, and is uncomfortable for the patient.

Bleeding after native and transplant renal biopsy has been previously identified by changes in the hematocrit, the presence of gross hematuria, transfusion requirements, the need for surgical intervention, and the presence of delayed hematoma formation as detected by ultrasound or computed tomographic scanning (5,8,9,20,23,24,26,27,29,30). The drop in hematocrit, transfusion requirement, and ultrasound findings immediately after biopsy were chosen as the determinants of bleeding in this study because these criteria have been previously well defined and are the least time consuming and most cost effective for use in clinical practice. Previous reports in renal transplant recipients have found that, on average, the hematocrit drops between 0 and 3 points within 24 h of the procedure and transfusion is required after 0 to 4% of biopsies (20,23,24,26,27,29,30). In this study, a drop in hematocrit of 4 points or more occurred in 25% of patients, ultrasound evidence of hematoma was seen in 2%, and transfusion was given in 0%. Gross hematuria was not analyzed because it occurred in only three patients, and both the BT and the TEG were unavailable in two of the three patients; thus, conclusions on the predictability of the coagulation assay for bleeding in the form of hematuria were not possible. Changes in hematocrit noted in this study appeared to be secondary to the biopsy procedure and not to fluid administration because most patients had not received exogenous fluids and those who had, received less than 500 mL.

Most patients in this study had normal coagulation results. Most reference ranges, including ours, are based on 95% confidence limits for the healthy population. Approximately 5% of healthy subjects will have results outside these limits. This is consistent with the results that we obtained. For each individual assay, 2 to 8% of the patients had an abnormal result. Altogether, 21% had at least one result outside the reference range. The problem with screening assays in this and previous studies is the low incidence of abnormalities in the population, the low predictive value of borderline abnormal results, and the high number of false-positives.

Of the coagulation assays evaluated, the TEG:angle and TEG:k values were the best predictors of bleeding. For patients with an abnormal TEG:angle, 5 (71%) of 7 bled after biopsy versus 24 (26%) of 94 bleeding with a normal TEG:angle (P < 0.01). An abnormal TEG:angle predicted an approximately threefold increase in the risk of mild bleeding after renal biopsy. In contrast, the bleeding time was not predictive of postbiopsy

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**TABLE 2. Predictive value of selected parameters for bleeding after biopsy**

<table>
<thead>
<tr>
<th>Assay</th>
<th>Sens (%</th>
<th>Spec (%)</th>
<th>PPV (%)</th>
<th>NPV (%)</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEG:Angle (degrees)</td>
<td>17%</td>
<td>97%</td>
<td>71%</td>
<td>74%</td>
<td>101</td>
</tr>
<tr>
<td>BT (min)</td>
<td>3%</td>
<td>95%</td>
<td>20%</td>
<td>72%</td>
<td>105</td>
</tr>
<tr>
<td>PT (s)</td>
<td>3%</td>
<td>91%</td>
<td>11%</td>
<td>70%</td>
<td>119</td>
</tr>
</tbody>
</table>

*Ability of tests to predict mild hemorrhage after renal biopsy. Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value. N, total number of tests evaluated. Bleeding was defined as a drop in hematocrit of 4 points or more 6 h after the procedure or ultrasound evidence of a new perirenal hematoma.*
bleeding. Further contrasts between the BT and TEG are noted by the fact that the BT may be prolonged when the TEG is normal. Aspirin injection causes no change in the TEG but results in prolongation of the BT (31–33). Uremia also prolongs the BT while increasing rather than decreasing TEG clot formation (34). Furthermore, uremia, which has long been associated with a prolongation of the BT, has not always been associated with increased bleeding after renal biopsy (5,23,24,35). As mentioned previously, prolonged BT on the forearm are not predictive of bleeding at other sites (11,36–39).

The lack of correlation between mild hemostatic abnormalities and postbiopsy bleeding can be explained by the fact that bleeding is probably more often determined by the vascular injury caused by the procedure than by the coagulation status of the patient. If the patient has no history or signs of prior bleeding, it is unlikely that they have a major undiagnosed abnormality. The most common occult coagulation abnormalities are low platelet counts, reduced platelet function, and reduced levels of vitamin K–dependent factors, either due to warfarin treatment, diet, or broad-spectrum antibiotic therapy. A simple screen for these potential problems is a TEG along with the history and physical examination. More serious deficiencies in coagulation, platelet, or fibrinolytic factors, however, may increase the risk for postbiopsy bleeding. The number of patients with moderate to severe abnormalities in our study is low, less than 1%. Much larger patient groups would be needed to determine clinical thresholds for bleeding for each test type. For example, on the basis of larger liver biopsy studies, it would appear that excess bleeding will probably not occur after liver biopsy if platelet counts are above 50,000/μL (28). Whether this result is applicable to native or transplant renal biopsy is unknown.

The TEG is an empiric assessment of overall hemostatic and fibrinolytic function (19,31). The r value is similar to a whole-blood clotting time; abnormal results indicate low levels of clotting factors and should be followed up with PT, PTT, and factor assays. The k value and angle indicate the rate at which the platelet/fibrin thrombus forms once initiated; abnormal results should be followed up with a PT, PTT, fibrinogen, and platelet count. The MA indicates maximum clot strength, which is a function of platelet count and fibrinogen. The A∞ should be compared with the MA; if a reduction of more than 5 to 10 mm is seen, it indicates the presence of significant fibrinolysis. A normal TEG indicates adequate levels of clotting factors, fibrinogen, and platelets with normal fibrinolytic activity.

Clinically, the TEG measurement has been shown to be more useful in the determination of bleeding after cardiac surgery and liver transplantation and is more reproducible than the BT (13,14,16). The use of the TEG during and after cardiac and hepatic procedures has also lessened the use of blood product support (13). The charge at our institution for performing a BT is $17.75; a platelet count is $7.00, and a PT and PTT together are $82.75. The charge for performing all of the above for 120 biopsies would be $8,940.00. The charge for a TEG ($17.25) for 120 biopsies would be $2,070.00. If we add to this the charge for additional workups on patients with abnormal TEG, we arrive at a total of $2,405, still far less than the prior workup while evaluating additional factors (i.e., fibrinolysis on the TEG).

In conclusion, the TEG appears to be the most cost-effective and predictive coagulation test to perform before a renal transplant biopsy. These tests should be used in conjunction with the bleeding history, medication history, and proper biopsy technique in order to minimize bleeding. An abnormality on the TEG should be further investigated by coagulation screening. After the coagulation defect is located, the biopsy could be canceled or coagulation product support could be arranged. Following these guidelines should help to reduce costs and minimize bleeding after renal allograft biopsy.

REFERENCES


