Bleeding Risk Assessment and the Role of Primary Hemostasis Screening in Patients Undergoing Kidney Biopsy

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ABSTRACT: **Background:** Risk factors for bleeding complications after percutaneous kidney biopsy (PKB) and the role of primary hemostasis screening are not well established.

Objectives: To determine the role of primary hemostasis screening and complication outcomes among individuals who underwent PKB.

Methods: We reviewed data of 456 patients who underwent PKB from 2010 to 2016 in a large university hospital. In 2015, bleeding time (BT) testing was replaced by light transmission aggregometry (LTA) as a pre-PKB screening test.

Results: Of the 370 patients who underwent pre-PKB hemostasis screening by BT testing, prolonged BT was observed in 42 (11.3%). Of the 86 who underwent LTA, an abnormal response was observed in 14 (16.3%). Overall, 155 (34.0%) patients experienced bleeding: 145 (31.8%) had minor events (hemoglobin fall of 1–2 g/dl, macroscopic hematuria, perinephric hematoma without the need for transfusion or intervention) and 17 (3.7%) had major events (hemoglobin fall › 2 g/dl, blood transfusion or further intervention). Abnormal LTA response did not correlate with bleeding (P = 0.80). In multivariate analysis, only prolonged BT (P = 0.0001) and larger needle size (P = 0.005) were identified as independent predictors of bleeding.

Conclusions: Bleeding complications following PKB were common and mostly minor, and the risk of major bleeding was low. Larger needle size and prolonged BT were associated with a higher bleeding risk. Due to the relatively low risk of major bleeding and lack of benefit of prophylactic intervention, the use of pre-PKB hemostasis screening remains unestablished.

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Percutaneous kidney biopsy (PKB) is an essential tool in the diagnosis and evaluation of kidney diseases [1]. The use of direct ultrasound guidance and automated spring-loaded biopsy devices has substantially improved the safety of the procedure [2]. However, despite these technical advances, PKB still confers a considerable risk of bleeding complications, with frequencies as high as 38% reported [3].

Several studies have identified risk factors for bleeding following PKB [4-6]; although the results are conflicting. Furthermore, only a few studies have addressed the role of primary hemostasis screening in this setting [3,7-9]. Bleeding time (BT) was the first test designed to evaluate in vivo primary hemostasis [10] and for predicting post-procedural bleeding [11]. While some investigations found an association between prolonged BT and bleeding complications after PKB [7,8], others reported an absence of such association [3,9]. Moreover, the invasiveness and low reproducibility of BT testing led some to advocate against its use as a preoperative screening test [12,13].

As platelet dysfunction is involved in the bleeding tendency of patients with kidney disease, various in vitro platelet function studies have been investigated as pre-PKB screening assays, yet results of their effectiveness have been conflicting [14,15]. Before 2015, the standard pre-biopsy hemostasis screening test at our center was BT testing. In 2015, light transmission aggregometry (LTA), which is currently considered the reference method for assessing platelet function [16], replaced BT testing in the setting of pre-PKB screening. The rationale for this change was derived from evidence from platelet aggregation studies of higher sensitivity in the detection of primary hemostasis defects [17,18].

In this study, we aimed to determine the role of primary hemostasis screening and complication outcomes among individuals who underwent PKB, before and after the switch of the screening method at our center (from BT testing to LTA). In addition, we aimed to identify risk factors associated with bleeding complications following PKB.

PATIENTS AND METHODS

DATA COLLECTION

We reviewed the medical records of all patients who underwent PKB between 1 January 2010 and 31 October 2016. Data extracted included patient demographics (age, gender), co-morbidities, indication for PKB, needle size, systolic and diastolic blood pressure, blood counts, serum creatinine, estimated glomerular filtration rate (eGFR), coagulation studies (prothrombin time [PT], partial thromboplastin time [PTT], and BT or LTA), prophylactic intervention, length of hospital stay, and bleeding events. eGFR was calculated based on the modified Modification of Diet in Renal Disease (MDRD) formula: $32788 \times \text{serum creatinine}^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if the patient was female). All retrieved and calculated information was recorded in an electronic database and analyzed.

Minor bleeding events were defined as a hemoglobin fall of 1–2 g/dl (confirmed by two consecutive blood counts), macroscopic hematuria or perinephric hematoma that did not necessitate blood transfusion or further intervention. Bleeding complications were deemed major if a hemoglobin drop greater than 2 g/dl was noted or if blood transfusion or further surgical or radiological intervention (including arterial embolization and bladder irrigation) was required to control bleeding [9,15]. Institutional review board approval waiving individual informed consent was obtained for this study from Hadassah Medical Center Helsinki Committee (No. HMO 0623-13).

KIDNEY BIOPSY PROTOCOL

Medical history, including bleeding diathesis and prescribed medications, were reviewed prior to PKB. Antiplatelet medications were discontinued 7 days prior to the biopsy. Similarly, oral anticoagulation therapy was discontinued and replaced by low molecular weight heparin, which was withheld the night before the biopsy. Patients were admitted to the hospital the day before the biopsy. Prior to the biopsy, vital signs, blood count, PT, activated PTT, and BT or light transmission aggregometry (LTA) were obtained. Based on the aforementioned test results, pre-biopsy intervention to improve hemostasis was performed at the discretion of the attending nephrologist, including the use of desmopressin (DDAVP), platelet or fresh frozen plasma transfusion, tranexamic acid, and dialysis. Pre-biopsy blood pressure above 150/90 mmHg was pharmacologically treated, whereas the biopsy was delayed when blood pressure was above 170/100 mmHg. All PKB were conducted by senior radiologists under continuous real-time ultrasound guidance with a 5-2 MHz broadband curved array transducer, using a Philips EPIQ 5 imaging system (Philips Medical System, Andover, MA, USA). PKB was performed according to a previously described technique [19]. A 16G or 18G automated biopsy needle (BioPince™, Argon Medical Devices, Plano, TX, USA) was used at the discretion of the radiologist. Patients were positioned flat in the supine position for 6–8 hours. All patients were monitored with nursing supervision for at least 24 hours after the biopsy. Routine assessment included frequent monitoring of vital signs, with blood count obtained at 6 hours after the biopsy and repeated on the following morning. Post-biopsy ultrasound and/or computed tomography scan were performed when a hemoglobin drop of > 1 g/dl or moderate to severe abdominal or flank pain were noted. Asymptomatic, hemodynamically stable patients were discharged the day following the biopsy.

PRIMARY HEMOSTASIS SCREENING ASSAYS

As part of the pre-biopsy evaluation, a primary hemostasis screening assay was performed in all patients: BT was the standard pre-biopsy hemostasis screening test before 2015, and LTA thereafter. BT testing was performed on the anterior surface forearm by means of a modified Ivy technique using a Surgicutt device (International Technidyne Corp, Edison, NJ, USA) [20]. BT was considered prolonged when the measurement was more than 9 minutes.

LTA was assessed using a standard aggregometer (PAP8, Bio/Data Corporation, Horsham, PA, USA), according to previously reported methods [21]. Briefly, the technique is based on the measurement of an increase in transmission of light through turbid platelet-rich plasma in response to the addition of exogenous platelet agonists. In our center, LTA was undertaken in response to adenosine diphosphate (ADP) (20 μmol/L), collagen (10 μg/ml), and epinephrine (100 μmol/L). LTA was considered abnormal when the maximum aggregation was below 40% in response to one of the agonists.

STATISTICAL ANALYSIS

Patient characteristics are described as proportions for categorical variables, mean ± SD for continuous variables that are normally distributed, and medians and interquartile range (IQR) for continuous variables that are not normally distributed. The association between two categorical variables was assessed by using either chi-square test or Fisher's exact test. The comparison of continuous variables between two independent groups was carried out using the two-sample *t*-test or the Mann–Whitney non-parametric test. A multivariate logistic regression model using the forward, stepwise, likelihood ratio method was applied to simultaneously assess the effect of factors independently associated with the development of bleeding, using significant factors from the univariate analysis in the model, with results reported as odds ratios (OR) and 95% confidence (95%CI) intervals. All tests applied were two-tailed, and a $P \leq 0.05$ was considered as statistically significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 22 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

PATIENT CHARACTERISTICS

During the study period, a total of 456 patients underwent PKB and were included in the study. Technical success (i.e., a specimen was produced) was achieved in all patients. Pre-PKB hemostasis screening included BT testing in 370 patients (81.1%) and LTA in 86 (18.9%). A summary of patient characteristics, stratified by the hemostasis screening test performed, is shown in Table 1.

The median age of this cohort was 47 (IQR 31–61) years. A male predominance was observed, with 269 males (59.0%) and 187 females (41.0%). Nephrotic syndrome was the most common indication for PKB (n=238, 52.2%), followed by hematuria-proteinuria (n=97, 21.3%), acute kidney injury (n=93, 20.4%), and nephritic syndrome (n=28, 6.1%). None of the patients had a clinical history suggestive of a significant bleeding disorder. Characteristics were comparable in patients for whom BT or LTA testing was performed. The median BT was 6.2 [5–7.3] minutes. Prolonged BT was observed in 42 (11.3%) of the patients in whom it was tested. Median LTA response for ADP was 71.5% (50.0–98.3%), for epinephrine 60% (38.7–79.5%), and for collagen, 69% (54–87%). Abnormal LTA response was detected in 23 patients (26.7%) in whom it was tested.

Prophylactic intervention to improve hemostasis was given in 10.5% (n=48) of the patients, including the administration of DDAVP (n=33), platelet transfusion (n=12), as well as fresh frozen plasma transfusion, tranexamic acid, and dialysis in one patient each. Prophylactic intervention was given to 37 patients with abnormal hemostasis screening: 76.2% (32/42) of those with prolonged BT and 21.7% (5/23) of those with abnormal LTA response.

BLEEDING COMPLICATIONS

Overall, 155 patients (34.0% of all patients) experienced at least one PKB-related bleeding complication, for a total of 199 bleeding events. Of them, 78 (50.3%) were men. Minor complications were experienced by 143 patients (31.4%), including a hemoglobin drop of 1-2 g/dl (n=85), perinephric hematoma (n=53), and macroscopic hematuria (n=41). Major bleeding events were encountered in 19 patients (4.2%), including a hemoglobin drop of >2 g/dl, blood transfusion (n=14), and bladder obstruction (n=6). No major events occurred that required surgical or radiological intervention. All patients were successfully managed conservatively without long-term sequelae. No deaths occurred as a direct result of a PKB bleeding complication.

Women were more likely to experience bleeding than men (41.2% vs. 29.0%, $P = 0.007$). Bleeding was more frequent among individuals who underwent kidney biopsy using 16G rather than 18G needles (44.2% vs. 28.4%, respectively, $P = 0.004$) [Table 2].

The overall rate of bleeding was comparable among those who underwent BT and LTA testing (34.1% vs. 33.7%, respectively, $P = 0.95$). A significantly higher proportion of patients with prolonged BT had bleeding events than patients with normal BT (50.0% vs. 31.9%, $P = 0.008$). In contrast, bleeding events occurred at similar rates among patients with abnormal and normal LTA responses (30.4% vs. 34.9%, $P = 0.80$) [Table 2]. Among patients with prolonged BT, rates* of bleeding were comparable between those for whom intervention was made and those for whom intervention was not made (56.3% vs. 40.0%, $P = 0.48$). Similarly, among patients with abnormal LTA, bleeding events occurred comparably among those for whom intervention was made and those for whom it was not (40.0% vs. 27.8%, $P = 0.62$). There were no other demographic, clinical, procedural, or laboratory value differences between patients with and without evidence of bleeding [Table 2]).

A multivariate analysis showed prolonged BT (OR 2.82, 95%CI 1.31–6.10, $P = 0.0001$) and larger needle size (OR 2.19, 95%CI 1.27–3.77, $P=0.005$) to be the only independent predictors of bleeding.

Acute kidney injury served as the indication for PKB for a higher proportion of patients with prolonged BT than for those with normal BT (35.7% vs. 16.8%, $P = 0.005$). Prolonged BT was more common among patients who underwent inpatient biopsy

Table 1. Baseline demographic, clinical and laboratory characteristics

	Bleeding time (n=370)	Light transmission aggregometry (n=86)	*P* value
Gender: male/female, n (%)	220/150 (59.5/40.5)	49/37 (57.0/43.0)	0.67
Age at biopsy, years	48 [31–61] (46)	44 [33–62] (46)	0.85
Indication for biopsy Nephrotic syndrome (%) Hematuria-proteinuria (%) Acute kidney injury (%) Nephritic syndrome (%)	 190 (51.4) 87 (23.5) 70 (18.9) 23 (6.2)	 48 (55.8) 10 (11.6) 23 (26.7) 5 (5.8)	0.07
Inpatient biopsy (%)	69 (18.6)	22 (25.6)	0.15
Transplanted kidney (%)	42 (11.4)	11 (12.8)	0.71
Diabetes mellitus (%)	68 (18.4)	20 (23.3)	0.30
Needle size, gauge (n=354) 18 (%) 16 (%)	 202 (70.6) 84 (29.4)	 48 (70.6) 20 (29.4)	0.99
Pre-biopsy systolic blood pressure, mmHg*	140 [127–150] (139)	138 [121–146] (136)	0.07
Pre-biopsy diastolic blood pressure, mmHg*	83 [75–90] (82)	79 [70–87] (80)	0.07
Pre-biopsy serum creatinine, µmol/L*	110 [72–168] (154)	98 [75–170] (162)	0.67
Pre-biopsy albumin, g/L*	36 [30–41] (35)	35 [30–42] (34.7)	0.92
Total protein in urine, gr*	2.6 [1.4–5.0] (3.8)	2.3 [1.1–3.5] (3.1)	0.12
Pre-biopsy MDRD eGFR, ml/min/1.73 m^2*	60.8 [37.2–99.0] (70.9)	64.3 [36.1–98.3] (71.2)	0.95
Pre-biopsy hemoglobin, g/dl*	12.4 [10.9–13.9] (12.4)	12.6 [10.9–14.1] (12.6)	0.56
Pre-biopsy hematocrit, %*	37.6 [33.0–41.6] (37.2)	37.5 [33.2–42.3] (37.9)	0.35
Pre-biopsy platelet count, ×10^9/L*	217 [178–261] (230)	213 [156–274] (220)	0.30
Pre biopsy prolonged PT/PTT (%)	57 (15.4)	11 (12.8)	0.62

*All continuous variables are expressed as medians [interquartile range] (mean)

LTA = light transmission aggregometry, MDRD eGFR = estimated glomerular filtration rate based on the MDRD formula, PT = prothrombin time, PTT = partial thromboplastin time

Table 2. Patient characteristics in relation to the occurrence of bleeding

	No bleeding (n=301)	Any bleeding (n=155)	*P* value
Gender: male/female (%)	191/110 (63.5, 36.5)	78/77 (50.3, 49.7)	0.007
Age at biopsy, years	46 [31-60] (46)	48 [29-62] (47)	0.74
Indication for biopsy Nephrotic syndrome (%) Hematuria-proteinuria (%) Acute kidney injury (%) Nephritic syndrome (%)	 163 (54.2) 63 (20.9) 62 (20.6) 13 (4.3)	 75 (48.4) 34 (21.9) 31 (20.0) 15 (9.7)	0.14
Inpatient biopsy (%)	56 (18.6)	35 (22.6)	0.31
Transplanted kidney (%)	39 (13.0)	14 (9.0)	0.22
Diabetes mellitus (%)	56 (18.6)	32 (20.6)	0.60
Needle size, gauge (n=354) 18 (%) 16 (%)	 179 (75.5) 58 (24.5)	 71 (60.7) 46 (39.3)	0.004
Pre-biopsy systolic blood pressure, mmHg*	140 [127–149] (139)	138 [125–150] (139)	0.86
Pre-biopsy diastolic blood pressure, mmHg*	83 [74–91] (83)	81 [74–89] (82)	0.44
Pre-biopsy serum creatinine, µmol/L*	103 [73–163] (148)	112 [74–180] (170)	0.21
Pre-biopsy albumin, g/L*	36 [31–41] (35)	36 [29–41] (34)	0.41
Total protein in urine, gr*	2.5 [1.4–5.0] (3.5)	2.4 [1.3–5.0] (4.0)	0.31
Pre-biopsy MDRD eGFR, ml/min/1.73 m^2*	64.4 [40.0–98.6] (72.3)	55.6 [32.4–98.5] (68.4)	0.39
Pre-biopsy hemoglobin, g/dl*	12.4 [10.8–13.9] (12.4)	12.6 [11.2–13.9] (12.5)	0.49
Pre-biopsy hematocrit, %*	37.2 [32.7–41.7] (37.2)	38.0 [34.1–42.0] (37.7)	0.39
Pre-biopsy platelet count, $\times 10^9$/L	213 [178–257] (225)	221 [168–276] (233)	0.35
Pre biopsy prolonged PT/PTT (%) *	48 (15.9)	20 (12.9)	0.41
Primary hemostasis screening test BT testing (%) LTA testing (%)	 244 (81.1) 57 (18.9)	 126 (81.3) 29 (18.7)	0.95
BT testing result** Normal (%) Prolonged (%)	 224 (91.8) 20 (8.2)	 104 (82.5) 22 (17.5)	0.008
LTA testing results*** Normal LTA (%) Abnormal LTA (%)	 41 (71.9) 16 (28.1)	 22 (75.9) 7 (24.1)	0.80

*All continuous variables are expressed as medians [interquartile range] (mean)

BT = bleeding time, LTA = light transmission aggregometry, MDRD eGFR = estimated glomerular filtration rate based on the MDRD formula, PT = prothrombin time, PTT = partial thromboplastin time

**Denominators represent the number of patients for whom bleeding time testing was performed

***Denominators represent the number of patients for whom light transmission aggregometry testing was performed

than among elective patients (21.7% vs. 9.0%, $P = 0.003$). eGFR levels below 30 ml/min/1.73 m^2 were also associated, although not with statistical significance, with prolonged BT (28.6% vs. 17.4%, $P = 0.08$).

DISCUSSION

During a 7 year period, bleeding complications occurred in 34% of patients who underwent PKB at one medical center. Most complications were minor. Larger needle size and prolonged BT were found to be independently associated with bleeding complications following PKB. Abnormal LTA response did not correlate with bleeding occurrence.

The role of pre-PKB primary hemostasis screening in predicting bleeding remains inconclusive. BT testing, which was the original test used to predict hemorrhagic risk in patients with kidney disease [22], was applied in the early years of our study period. The higher risk of bleeding for patients with prolonged BT, reported here, is in accordance with other studies [7,8]. Nevertheless, due to the limitations of BT testing, and despite its apparent clinical utility, other methods of detecting defects in primary hemostasis have been developed. In our medical center, LTA, which replaced BT testing, did not correlate with post-PKB bleeding events. This finding challenges the use of LTA as a screening test in this setting. As multifactorial pathophysiologic mechanisms (e.g., endothelial dysfunction, co-morbidities) are involved in bleeding diathesis in patients with renal dysfunction [23], testing only platelet aggregation may not reliably reflect the hemostatic state of these patients.

In our study, patients who had pre-biopsy prolonged BT were almost three times more likely to experience bleeding than were those with normal BT results. Nevertheless, among patients with prolonged BT, pre-procedural intervention to improve hemostasis did not result in a decreased bleeding risk. This finding concurs with previous studies [7,9]. Therefore, it remains unclear whether increased BT has any causal effect on bleeding. Future prospective studies are warranted to evaluate the role of prophylactic intervention to improve BT in the prevention of bleeding complications after PKB.

The association between biopsy needle size and the risk of bleeding is controversial. While smaller studies have failed to demonstrate such association [4,5,24], a recent meta-analysis reported that larger needle size confers a higher risk of transfusion after PKB [6]. In our cohort, the use of 16G compared to 18G needles was an independent predictor of post-PKB bleeding. Nevertheless, considering that most bleeding events were minor, together with the concern for reduced diagnostic yield using smaller size needles [25], we cannot advocate against the use of 16G needles.

In our cohort, women were at greater risk of bleeding complications than men, according to a univariate analysis. This concurs with studies that demonstrated higher risk among women for either major or minor bleeding complications following PKB [4,6,8]. Smaller kidney size in women was suggested to result in deeper penetration of the needle during PKB, thereby potentially injuring a larger number of blood vessels [6]. Moreover, the greater proportion of fat mass in women may lead to hemorrhagic expansion into perinephric adipose tissues [4].

Limitations of the present study include its retrospective design and the biases inherent to such data collection. In addition, the complication risk is certainly underestimated, as systematic post-biopsy imaging surveillance was not rou-

tinely performed. Furthermore, we did not include a control group in which no pre-biopsy hemostasis screening test was performed. Finally, our study is a single-center study, which may limit the applicability of our results to hospitals with different populations of patients.

CONCLUSIONS

In this evaluation of bleeding complications following PKB, we identified larger needle size and pre-biopsy prolonged BT as the only independent risk factors for the occurrence of bleeding. As abnormal platelet aggregation studies did not correlate with bleeding, their use as a screening method in this setting should be discouraged. Despite the association of prolonged BT with bleeding complications, we cannot recommend its routine use in this setting. This conclusion is due to the lack of benefit of prophylactic intervention and the relatively low risk of major bleeding. Larger prospective studies are needed to better delineate the role of pre-biopsy hemostasis screening, to further evaluate risk factors for bleeding, and to formulate optimal prophylactic strategies.

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Capsule

An alternative treatment for leukemia

In some acute myeloid and juvenile myelomonocytic leukemias (AMLs and JMMLs), tumor growth is driven by activating mutations in the phosphatase PTPN11. **Jenkins** and colleagues found that mutant PTPN11 activity is enhanced by the kinase TNK2. The multikinase inhibitor dasatinib decreased TNK2 and mutant PTPN11 activity and downstream proliferative pathways in cultured patient cells. It also extended survival in a JMML patient with mutant PTPN11. Thus, dasatinib, which is clinically approved for the treatment of other leukemias, could potentially slow disease progression in AML and JMML patients.

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