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MINIREVIEWS

Renal biopsy practice: What is the gold standard?

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Abstract

Renal biopsy (RB) is useful for diagnosis and therapy guidance of renal diseases but incurs a risk of bleeding complications of variable severity, from transitory haematuria or asymptomatic hematoma to life-threatening hemorrhage. Several risk factors for complications after RB have been identified, including high blood pressure, age, decreased renal function, obesity, anemia, low platelet count and hemostasis disorders. These should be carefully assessed and, whenever possible, corrected before the procedure. The incidence of serious complications has become low with the use of automated biopsy devices and ultrasound guidance, which is currently the "gold standard" procedure for percutaneous RB. An outpatient biopsy may be considered in a carefully selected population with no risk factor for bleeding. However, controversies persist on the duration of observation after biopsy, especially for native kidney biopsy. Transjugular RB and laparoscopic RB represent reliable alternatives to conventional percutaneous biopsy in patients at high risk of bleeding, although some factors limit their use. This aim of this review is to summarize the issues of complications after RB, assessment of hemorrhagic risk factors, optimal biopsy procedure and strategies aimed to minimize the risk of bleeding.

Key words: Renal biopsy; Bleeding; Complications; Procedure

Core tip: Renal biopsy (RB) is useful for diagnosis, prognostic assessment and therapy guidance of various diseases affecting native kidneys or transplants. However, RB incurs a potential risk of bleeding complications of variable severity. This aim of this review is to summarize the issues of complications after RB, assessment of hemorrhagic risk factors, optimal biopsy procedure and strategies aimed to minimize the risk of bleeding.

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INTRODUCTION

Renal biopsy (RB) is often necessary for diagnosis, prognostic assessment and therapy guidance of various diseases affecting native and transplant kidneys. The final diagnosis differs from the main hypothesis in up to one third of cases[1]. Despite its necessity, RB incurs a potential risk of bleeding complications of variable severity, from transitory hematuria or asymptomatic hematoma to life-threatening hemorrhage[1-3]. Several studies identified risk factors for complications after RB[4-6]. However, controversies persist regarding the optimal assessment and management of bleeding risk. Two surveys, one conducted by the Society of Nephrology in France and another one in United Kingdom paediatric hospitals, highlighted significant variation in RB procedures[7,8]. Therefore, the gold standard for RB practice still re-

mains to be defined. We previously participated to the elaboration of consensual recommendations by the Society of Nephrology in France[8]. Optimizing procedures for RB may improve patient safety and may also provide some logistic benefits and save costs.

This review discusses the issue of complications after RB, optimal biopsy procedure, and strategies aimed to minimize the risk of bleeding. We only address biopsies for the investigation of medical kidney diseases, but not those performed for kidney tumors.

COMPLICATIONS AFTER PERCUTANEOUS RB

Several large prospective and retrospective studies provide an estimate of the frequency of complications after percutaneous RB[1-3,5,9-12]: (1) Death: < 0.1%; (2) Major bleeding requiring nephrectomy or surgical hemostasis: 0.1% to 0.5%; (3) Arteriovenous fistula requiring invasive intervention: 0.1% to 0.5%; (4) Blood transfusion requirement: 0.3% to 7.4%; (5) Uncomplicated hematoma: 10 to 90%; and (6) Transient macroscopic hematuria : 1% to 10%.

We recently published a series of 312 native kidney biopsies performed at our institution: 15% of patients developed a symptomatic hematoma, 5% macroscopic hematuria, 9% received a red blood cell transfusion and 1% required an angio-intervention[13].

The reported incidence of complications after RB varies in relation to numerous factors, including patient selection, definitions of complications, procedures, and monitoring protocols. Several studies were performed before the implement of ultrasound guidance and automated biopsy devices, which improved the safety and efficiency of RB procedures[4,9]. The rates of complications drawn from these reports may therefore not reflect the risk associated with RB performed nowadays.

Recent studies reported major bleeding and life-threatening complications in less than 0.1% of RB procedures[2,4]. Tøndel *et al*[12] recently published the largest report of RB complications: 9288 (715 children and 8573 adults) biopsies from the Norwegian kidney biopsy registry, the vast majority of which (99.7%) were guided by ultrasound. In this study, 0.9% of the patients needed blood transfusion, 0.2% required an invasive procedure (surgery or angiointervention), and 1.9% had a macroscopic hematuria[12].

The risk of bleeding complications appears lower for transplant than native kidney biopsie[14,15]. However, major complications can occur after transplant biopsy[16].

ASSESSMENT OF HEMORRHAGIC RISK FACTORS AND CONTRAINDICATIONS TO PERCUTANEOUS RB

An important step before RB is to search for factors increasing the risk of complications, particularly bleeding. Although there are no definitive ways to predict which patients will experience complications, several predisposing factors to bleeding have been identified, at times inconstantly.

High blood pressure, age, a decreased GFR, obesity, anemia, low platelet count and small center size (< 30 biopsies/year) are associated with an increased risk of bleeding[4-6,12,17-19]. Amyloidosis was reported to be associated with bleeding[4], although such association was not found in large study by Tøndel *el al*[12]. As discussed below, hemostasis disorders, anticoagulant or antiplatelet therapy, and certain anatomic conditions, may also contraindicate or complicate percutaneous RB.

A recent systematic review and meta-analysis of hemorrhagic complications after percutaneous native kidney biopsy using ultrasound guidance and automated spring-loaded biopsy device reviewed 34 publications and concluded that the predictors of erythrocyte transfusion were: the needle gauge (14 *vs* 16 or 18), sex (female), serum creatinine (⩾ 2 mg/dL), low hemoglobin prior biopsy (⩽ 12 g/dL) and acute kidney injury[18].

High blood pressure

Although high blood pressure is a well-recognized and modifiable risk factor of bleeding after RB[4,6,19], it is difficult to determine a cut-off level above which RB should not be performed. One study demonstrated a significant increase in the risk of bleeding when systolic blood pressure (SBP) was > 160 mmHg or diastolic blood pressure (DBP) was > 100 mmHg[6]. Some studies suggested that an upper limit value of 140/90 mmHg prior to an RB procedure would be appropriate to minimize this risk[4,6]. Interestingly, the risk of bleeding is increased in patients with a history of hypertension, irrespective of blood pressure at the time of biopsy[6]. It is possible that arteriolar hyalinosis associated with chronic hypertension limits the ability of vessels to contract following RB, regardless of the current blood pressure.

Hemostasis abnormalities

Screening for inherited or acquired hemostasis abnormalities relies on patient questioning, study of current and recent medications, and hemostatic tests. Even patients with mild bleeding disorders can bleed after surgery or invasive procedures[20]. In the general population, the most frequent mild bleeding disorders are Von Willebrand disease and platelet function disorders, each with an estimated frequency of up to 1%[21]. Thus, questioning patients about personal and familial bleeding history should not be neglected. However, our survey conducted in France highlighted that such information was not always assessed[8]. One issue may be that nephrologists are not familiar with this practice. The use of questionnaires prepared by hemostasis experts, such as the bleeding assessment tools[21] may be helpful to screen for inherited hemostasis abnormalities. However, these tools have not been validated in the setting of RB and cannot be used to predict bleeding after RB.

Careful examination of the list of current and recent medications, with a focus on anticoagulant and antiplatelet drugs, should be systematically performed before RB. The issue of RB in patients receiving anticoagulant or antiplatelet is discussed below.

It is universal practice to check blood cells count, prothrombin time and partial thromboplastin time before RB[8]. When a bleeding disorder is suspected based on a history of previous bleeding episodes, thrombopenia or abnormal hemostasis tests, thorough investigations should be carried out to determine whether percutaneous RB can be performed safely. It should be emphasized that hemostasis laboratory tests available do not reliably predict "uremic bleeding", which is the result of multifactorial alterations of hemostasis in a setting of chronic or acute renal failure[17]. Some nephrologists use bleeding time in an attempt to predict complications after RB, and some studies showed that a prolonged bleeding time was a risk factor for hemorrhagic complications[19]. However**,** the usefulness of this test is controversial. In the context of RB, several studies failed to demonstrate predictive value of the bleeding time for hemorrhagic complications[3,4,22,23]. It is now widely accepted that the bleeding time is not a good predictor of the risk of hemorrhage associated with surgical procedures and cannot reliably identify patients who have recently ingested antiplatelet agents; it is therefore no longer recommended as a routine preoperative test[24,25]. *Other laboratory* hemostasis tests have not been shown to improve prediction of bleeding after RB and are therefore not required.

RB in patient receiving anticoagulant or antiplatelet therapy

It is a standard of care to discontinue anti-platelet agents and non-steroidal inflammatory agents 5 to 7 d before an invasive procedure in order to reduce the risk of bleeding. However stopping an anti-platelet agent in a coronary patient can increase the risk of a thrombotic event[26], especially in patients with a high cardiovascular risk profile (extensive coronary disease, patients with recent stent placement: less than 6 wk after bare metal stent placement and less than 6 to 12 mo after drug eluting stent placement)[27,28]. In a cohort of 1358 consecutive patients admitted for a suspected acute coronary syndrome (ACS), 5% of those patients with a confirmed ACS had a history of coronary artery disease and had recently stopped their aspirin. The event happened after a mean of 11 d of aspirin cessation[29].

Some studies raised the possibility that withdrawal of antiplatelet therapy might not be mandatory before RB. In a retrospective study, the incidence of major hemorrhage after percutaneous RB was 1% (13/1270) in patients taking aspirin before RB, which was similar to the incidence of bleeding in patients not taking aspirin[30]. One important limitation of this study was that patients who stopped aspirin less than 10 d before RB, which is a common practice, were included in the "aspirin use" group. Additionally, the continuation of an anti-platelet agent was not identified as an increased risk factor of blood transfusion in a meta-analysis of 34 studies[18]. Mackinnon *et al*[31] reported 1120 RB from two different centers, in one, anti-platelets were stopped 5 d before the biopsy, whereas they were not discontinued in the other. There were no difference in the rate of major complications between the two centers but a significantly higher percentage of patients in the group still taking anti-platelet agents experienced a $\geqslant$ 1g/dL reduction in hemoglobin (23.5% *vs* 12.5%). The proportion of patients taking an anti-platelet agent was only specified for the elective biopsies (135 patients) where 75 had stopped the agents prior to biopsy whereas 60 patients were still taking an anti platelet agent (aspirin $n = 68$, clopidogrel $n = 7$) at the moment of the biopsy[31].

However, these studies about the safety of RB without cessation of aspirin have important limitations. In addition, the risk of bleeding associated with the continuation of other agents such as clopidogrel or newer agents like prasugrel or ticagrelor, is higher than the one with aspirin. It should be kept in mind that RB is a high bleeding risk procedure and, in our opinion, withdrawing anti-platelet agents before RB should be the standard of care in low-risk patients. It is therefore advisable to withhold these agents for 7 d before an elective kidney biopsy[32], and resume them 1 to 2 d after the biopsy. The management of patients at high risk of thrombotic events should be discussed with their cardiologist. The biopsy should be deferred if necessary or a transjugular biopsy, if available, should be considered.

Oral anticoagulant (anti-vitamin K) should be stopped 5 d before the biopsy and bridging with heparin should be considered in high and moderate risk patients. Oral anticoagulants should be resumed 12 to 24 h after the biopsy[28].

Although data are limited, platelet transfusion seems to be the best option in patients who are taking an anti-platelet agent and experience severe bleeding from a RB.

Solitary kidney and anatomic abnormalities

Renal ultrasound is usually performed in the assessment of kidney diseases and provides important information before RB about the size and morphology of kidneys. An anatomic or functional solitary native kidney is generally considered as a contraindication for RB, given the possibility that nephrectomy may be necessary in case of life-threatening bleeding. Complications requiring nephrectomy are however very rare and ultrasound-guided percutaneous RB with an automated biopsy device has been shown to be safe if contraindications, especially high blood pressure and abnormal haemostasis, are adressed. In three retrospective studies that included a total of 1955 ultrasound-guided percutaneous renal biopsies, only one case required nephrectomy[2-4]. Some authors advocated that otherwise uncomplicated adult patients with a solitary kidney might be considered for percutaneous biopsy[5]. Despite these reassuring data, un-

dertaking a solitary kidney biopsy remains an important decision that should be made only after carefully thinking about whether the RB result is likely to have important therapeutic implications.

Anatomic abnormalities of the kidney (congenital malformations, cysts, atrophy, hydronephrosis...) or blood vessels (arteriovenous fistula, aneurysm, microaneurysm...) can make RB difficult to perform. Such abnormalities have to be carefully characterized using appropriate imaging techniques in order to determine the risk and feasibility of the biopsy.

PREVENTION OF BLEEDING BEFORE RB

As it is for any invasive procedure, correction of coagulopathy is mandatory before RB. The platelet count threshold at which a RB can be safely conducted is not clear. Most platelet count thresholds for invasive procedure are based on weak observational evidence. For most major surgery, other than ocular and neurologic, platelet transfusion are considered if the platelet count is below 50000/microL[33]. It is not clear if this can be applied to RB. Many nephrologists consider RB contraindicated if platelet count is < 100000/microL, which seems more prudent. Of course, optimal methods for raising platelet count depend on the underlying condition.

In the setting of renal disease, the risk of bleeding can result from dysfunctional platelets resulting from uremia. Indeed, uremic bleeding is a well-known complication of renal failure. The exact underlying mechanisms remain largely unknown, but seem to be multifactorial. The pathophysiology of uremic bleeding and evidence based treatment recommendations were the subject of a review by Hedges *et al*[17]. Many factors contribute to platelet dysfunction including anemia, dysfunctional von Willebrand factor, platelet membrane abnormalities, uremic toxins inhibiting platelet aggregation, and increased prostacyclin and nitric oxide levels, which are strong anti-platelet aggregating factors[17]. Correction of anemia, deamino-8-D-arginine vasopressin (DDAVP), estrogens and cryoprecipitate have been shown to improve "uremic bleeding".

Desmopressin (DDAVP) is probably the most common agent used to treat or prevent bleeding in uremic patients. DDAVP improves hemostasis by releasing factor VIII from storage sites. DDAVP can reverse uremic platelet dysfunction rapidly (approximately within one hour of IV injection) for a short period of time (around 24 h)[17].

Several studies demonstrated that recombinant erythropoietin treatment prevents bleeding caused by uremic platelet dysfunction if the hematocrit is increased to more than 30%. Recombinant erythropoietin was shown to improve primary hemostasis in uremia through an increase of hematocrit but also through an effect on platelet function[17,34,35].

Several studies showed that intravenous conjugated estrogens can safely and effectively improve uremic platelet dysfunction and clinical bleeding. Intra-venous conjugated oestrogens improve bleeding time with a maximum effect at 5 to 7 d, lasting from 14 to 21 d[17].

Finally, cryoprecipitate is another therapeutic option in the setting of active uremic bleeding or in patients with high risk of bleeding[17,36]. Cryoprecipitate is prepared from plasma and contains fibrinogen, von Willebrand factor, factor Ⅷ and factor XⅢ. It has a rapid onset of action (around 1 h) and its effect lasts approximately 24 to 36 h.

The impact of dialysis on uremic bleeding is unsure. Studies are old, and the effect on platelet function and coagulation is inconstant.

In all, the evidence supporting recommendations for the prevention or treatment of uremic bleeding is limited, especially in the context of RB. Despite the absence of robust evidence, it may be prudent to avoid undertaking RB when the hematocrit is lower than 30%, and to consider DDAVP or oestrogens before RB when the glomerular filtration rate is lower than 30 mL/min per 1.73m^2, as suggested by some authors[37].

PROCEDURES FOR PERCUTANEOUS RB

Well-trained nephrologists can perform RB as well as radiologists[38,39]. Automated biopsy guns have superseded Tru-cut needles and are probably used in most centers[8]. Several studies suggested that 14-18G needles are appropriate for percutaneous RB[3,15,40]. The use of an automated biopsy gun in combination with real-time ultrasound guidance was reported to provide adequate samples in nearly 99% of cases, with severe hemorrhagic complications occurring in less than 0.1%. This method can be considered the gold standard[2,4]. The use of bedside ultrasound to assess the location and depth of the kidneys was reported as a reliable alternative to real-time guidance[39]. In some instances, especially in obese patients, it may be necessary to perform RB under guidance by CT-scan instead of ultrasound.

ALTERNATIVES TO PERCUTANEOUS RB

Transjugular RB has been reported to be a safe and reliable alternative to conventional percutaneous RB in patients with obesity[41] or those at risk for bleeding, including high-risk patients with coagulopathy and thrombocytopenia[42-44]. In these studies, transjugular RB provided diagnostic yield and safety similar to those of percutaneous approach. However, in most countries, the use of transjugular RB is limited to a few centers because of the necessity of skilled interventional radiologists.

Laparoscopic RB has also been reported as an alternative for patients in whom percutaneous approach was not feasible or was contraindicated, because of obesity, solitary kidney, anticoagulation or coagulopathy, or failed percutaneous biopsy[45,46]. However the number of patients included in these studies was limited and no study has compared the safety of percutaneous, transjugular

Table 1 Studies evaluating the safety of short observation time (< 24 h) after a percutaneous renal biopsy of native kidney

Study	Complications: minor/major	Timing of complications
Whittier *et al*[22] Retrospective 750 patients	6.6% minor complications 6.4% major complications (79% blood transfusion)	38 (42%) complications ⩽ 4 h post RB 61 (67%) complications ⩽ 8 h post RB 77 (85%) complications ⩽ 12 h post RB 81 (89%) complications ⩽ 24 h post RB
Lin *et al*[56] Retrospective 147 inpatients 183 outpatients	19.7% hematoma 6.4% macroscopic hematuria 0.9% pain No difference between in and out patients	2 outpatient admission (blood transfusion) all complications occurred within observation time of 6 h
Maya *et al*[57] Prospective *N* = 100	13% asymptomatic hematoma No major complications	All complications occured within 8 h of observation time 4% extended 24 h observation for decrease hematocrit
Margaryan *et al*[53] Retrospective, *N* = 146	Bleeding 2.8% Gross hematuria 1.4% Transfusion 0.69%, intervention 0	Hospital admission 5.6%, no late complications. Observation time 4-6 h
Jiang *et al*[52] Retrospective *N* = 475	6.9% minor complications 1.3% (6 patients) had major complications (transfusion or interventional radiology)	Median time for minor complications 2.5 h, 4/33 after 6 h 4/6 major complications occurred within 4 h, 1/6 at 12 h and 1/6 beyond 48 h
Carrington *et al*[50] Retrospective *N* = 192	3.6% (*n* = 7) immediate complications related to bleeding, 2/7 required blood transfusion and embolisation	All complications occurred within observation period of 8 h
McMahon *et al*[31] Prospective *N* = 105, low risk	11% required admission for complications (11/12 minor, 1 major complication)	9/12 during the observation time (5 h) 1 at 48 h (macroscopic hematuria), 2 at 5 d (AVF, hematoma)
Simard-Meilleur *et al*[13] Retrospective 164 inpatients 148 outpatients	15% symptomatic hematoma (pain, drop of more than 10 g/l Hb, gross hematuria, hypotension), 9% RBC transfusion, 1% angio-intervention	100% outpatient complications occurred during observation time (8 h)
Korbet *et al*[19] Prospective 1055 patients	Minor complications 8.1% Major complications 6.6%	57% of all complications occurred within 4 h, 72% within 8 h, 85% within 12 h and 89% within 24 h

RB: Renal biopsy.

and laparoscopic RB in patients at high risk for bleeding. In addition, when considering these procedures, one should carefully contemplate the risk of general anesthesia, perioperative risk and recovery time.

SURVEILLANCE AFTER RB

After RB, patients have to be monitored closely for the occurrence of complicatons such as gross hematuria, flank pain, hypotension and acute renal obstruction.

The standard practice after RB has traditionally been to observe the patient overnight, as suggested by early studies[47]. In our French survey, almost all nephrologists observed patients for at least 24 h after a native kidney biopsy[8]. However, controversies have emerged regarding the optimal duration of observation after RB and it has been proposed that patients be discharged after 6-8 h of observation[48,49]. Performing RB as an outpatient procedure offers several advantages but raises the concern of missing late complications. Whittier *et al*[22] reported a large series of 750 native kidney biopsies in adults. In this study, 13% patients developed biopsy-related complications; minor complications occurred in 6.6% and major complications (most requiring a blood transfusion) occurred in 6.4% patients. Around 30% of the patients had a biopsy performed using a manual biopsy device. The analysis of the timing of complications showed that 89% of complications were identified within 24 h after RB, and that an observation period less than 8 hours missed 33% of complications. On the contrary, several smaller studies suggested that outpatient observation time of 6 to 8 h is safe (Table 1)[13,19,49-57]. Most of outpatients in these studies were selected as low risk. Considering this, an outpatient biopsy may be an option in a carefully selected population with no risk factor.

Renal transplant biopsies are routinely performed as an outpatient procedure in some centers. In our survey in France, approximately 25% of nephrologists performed transplant biopsies with observation times limited to 4-8 h[8]. In a multicentric study by Furness *et al*[58] on 2127 protocol transplant biopsies, only 9 (0.42%) severe complications occurred, all presenting within four hours after biopsy. In another study, no severe complications were observed after 251 protocol transplant biopsies[59]. Therefore, an observation time of 4-8 h after a transplant biopsy appears to be a relatively safe practice, at least in patients without risk factors for bleeding.

Some protocols use a routine renal ultrasound or measurement of hemoglobin or hematocrit control before discharge, in addition to clinical monitoring. Systematic ultrasound reveals perirenal hematoma in 40%-90% of procedures[11,60]. Arteriovenous fistula may be detected in 10% of RB, but they usually disappear

spontaneously after a few months[61,62]. In biopsies that are otherwise uncomplicated with an asymptomatic course, hematomas are usually small (< 3 cm)[48,63]. These hematomas are almost always asymptomatic, and such a finding usually occurs without therapeutic consequence. In a study that evaluated the use of renal ultrasound one hour post-RB, the presence of a hematoma was poorly predictive of complications[63]. The absence of a hematoma was predictive of an uncomplicated course in after RB[63]. However, a period of observation is required after RB, even in the absence of hematoma right after the biopsy. Early routine repeat imaging is therefore of limited usefulness and is not necessary in patients otherwise asymptomatic.

The use of a hemoglobin or hematocrit measurement after a RB as a predictor of bleeding is controversial. Systematic hemoglobin monitoring was shown to be of little value in detecting complications after RB in one study[22], although in another study, a direct relationship was found between the change of hematocrit at 6 h and the hematocrit at 24 h following a RB, suggesting that the absence of fall at 6 h makes a significant fall of hematocrit at 24 h unlikely[64].

CONCLUSION

The RB is an indispensable tool to establish the diagnosis and management of kidney diseases. Although the overall incidence of serious complications is low, risk factors for bleeding must be carefully assessed and, whenever possible, corrected before the procedure. If contraindications, especially high blood pressure and hemostasis abnormalities, are respected, percutaneous RB with an automated biopsy device and ultrasound guidance is safe for the vast majority of patients. Some controversies remain regarding the optimal duration of observation and the possibility to perform RB as an outpatient procedure. To address these issues, further studies are warranted to improve our ability to predict and stratify the risk of bleeding.

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