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Editorial Comment

EDITORIAL COMMENT

Renal biopsy: it is time for pragmatism and consensus

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ABSTRACT

To obtain truly informed consent, we must be able to advise our patients accurately about the relative risk and benefit of any treatment plan. Percutaneous renal biopsy remains the gold standard investigation in the evaluation of intrinsic renal disease. There have been significant improvements in practice over the past decades with regards to percutaneous renal biopsy. Across centres, we appear now to have reached agreement on many aspects of this procedure, such as the need for blood pressure control, avoidance of coagulopathy, use of spring-loaded needles under direct imaging guidance and a need to monitor for complications. The authors from Rush University Medical Centre provide reassurance that renal biopsy in the modern era remains a safe procedure with a low rate of significant bleeding. There remain areas of divergence in practice that may have unintended and deleterious consequences: administration of desmopressin and discontinuation of aspirin, for example, both carry a risk of thrombosis. It is our opinion that it is time to reach consensus on our interpretation of the available data and to draw up guidelines to standardize our biopsy practice internationally.

Keywords: aspirin, biopsy, bleeding, complication, renal

INTRODUCTION

To obtain truly informed consent, we must be able to advise our patients accurately about the relative risk and benefit of any treatment plan. Percutaneous renal biopsy remains the gold standard investigation in the evaluation of intrinsic renal disease. The use of spring-loaded biopsy needles under direct radiological (commonly ultrasound) guidance is now standard practice. These needles boast a more favourable risk profile compared with the older Tru-Cut or Vim-Silvermann devices; significant complications that threaten the life of the patient or the kidney are rare. Here, we describe the findings of two studies from Rush University Medical Centre and discuss the current evidence and its limitations regarding the interpretation of bleeding risk in advance of renal biopsy.

Bleeding complications after renal biopsy

In this issue of CKJ, the group from Chicago present findings from their biopsy practice spanning two decades. Whittier *et al.* [1] look at the risk of complications in native versus transplant renal biopsies from 1995 to 2015, whilst Korbet *et al.* [2] compare the risk of complications in patients undergoing native renal biopsy for acute kidney injury (AKI) versus other indications from 1991 to 2015. All biopsies were conducted with modern spring-loaded biopsy needles: 88% of native biopsies were conducted using 14-gauge needles; the remaining native and all transplant biopsies used 16-gauge needles. Patients undergoing biopsy were generally expected to have controlled blood pressure and normal clotting parameters, including prothrombin time, activated partial thromboplastin time and bleeding time. In patients with abnormal bleeding time, desmopressin was administered in some cases at the discretion of the responsible physician. A major bleeding complication was defined as bleeding requiring intervention: surgery, interventional radiology procedure, readmission, blood transfusion or death.

Whittier *et al.* [1] report excellent diagnostic yield: 92% of 767 native and 88% of 938 renal transplant biopsies contained at

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least 10 glomeruli, with adequate tissue for diagnosis in over 99% of cases. The rate of major complications or blood transfusion alone were 5.9 and 5.2%, respectively, in native renal biopsies, and 3.8 and 3.3%, respectively, in renal transplant biopsies. These complication rates are higher than in other published series [3–7], and blood transfusion accounts for the majority. This may reflect differences in biopsy or transfusion practices in this centre compared with other units. For example, authors from this centre have reported previously that around half of all blood transfusions were administered for haematoma (regardless of starting haemoglobin level), and routinely undertake ultrasound screening at 1 h post-biopsy [8]. Second, the routine use of 14-gauge biopsy needles for native renal biopsy may be associated with a higher rate of bleeding complications [9–11]. Third, smaller centre size (performing fewer than 30 biopsies per year or 1 per week) has been associated with greater complication rate [5]. Whittier *et al.* describe data from a centre in which an average of 37 native and 47 transplant biopsies were conducted per year. For comparison, the rate of major complication in our centre is 2.2% (1.8% transfusion): we conduct >170 native kidney and 80 transplant biopsies per year, of which >90% are performed by nephrology trainees [3]. Finally, the authors routinely observe patients after native biopsy for 24 h and transplant biopsy for 8 h. Whittier *et al.* acknowledge that asymptomatic patients observed overnight may undergo further investigation for a bleeding complication based on laboratory results. The clinical significance of this is unclear.

Korbet *et al.* [2] report data on the rate of major complication following native renal biopsy for AKI versus other indication. Of 955 native renal biopsies reviewed, 160 (16.8%) were undertaken for AKI. Patients biopsied for AKI were older (58 versus 44 years) and had higher serum creatinine (4.5 versus 1.8 mg/dL), lower haemoglobin (10.4 versus 12.2 g/dL) and a greater proportion had clotting abnormalities. There was a higher rate of major complication seen in the AKI group, compared with the group biopsied for other indications [11.3 versus 6.7%; odds ratio 1.78, 95% confidence interval (CI) 1.01–3.12]. Perinephric haematoma was common, occurring in 72.2% of the AKI group and 79.2% of non-AKI patients, which again may reflect routine ultrasound screening at 1 h. There was a high proportion of blood transfusion in patients biopsied for AKI (10.0% versus 5.1%, $P = 0.02$). Lower haemoglobin, female gender, increased systolic blood pressure and higher serum creatinine were risk factors for major complication in this group on multivariate analysis.

Patients were routinely observed for complication for a 24-h period after native biopsy and 8 h after transplant biopsy in this centre; the proportion of complications occurring beyond an 8-h window after biopsy were similar for both native (28%) and transplant (26%) biopsies. Reassuringly, the absolute number of complications requiring readmission was small: fewer than 7 readmissions per year for native renal biopsies; 10 readmissions per year for transplant. The authors point out that an extended period of observation likely increases the detection of complications, and therefore the proportion of complications detected beyond 8 h, which might otherwise be missed. This is corroborated by other reports with up to a third [12, 13] and up to 12.5% [14, 15] of complications detected beyond 8 h in patients undergoing native and transplant biopsy, respectively. Serious complications can present late and without early features of concern. Redfield *et al.* [15] reported time to any complication of 5.6 h (SD 13.8), but time to severe or life-threatening complication of 12.4 h (SD 12.1)—54% of these developing beyond 8 h—though with significant variability from the mean. We do not know the clinical impact of a complication occurring out of hospital versus in hospital, and whether the former has deleterious effects on patient outcome. Indeed, day-case procedures are commonly undertaken in some centres (including our own) without increased risk of complications [3, 16–18]. We must be pragmatic and balance the relative risk of complication with the expense and alternative risks of an extended hospital stay.

Unintended consequences

The authors report that they occasionally administer desmopressin (DDAVP) to correct bleeding time [1] and it is their routine practice to withhold aspirin prior to renal biopsy [8]. While both practices are common there is no clear consensus on the correct approach to these issues. Both administering desmopressin and withholding aspirin may have unintended, harmful consequences for the patient.

Desmopressin and bleeding time

Desmopressin, a vasopressin analogue, is licensed for use in patients with haemophilia A and von Willebrand's disease to reduce clinically significant bleeding. It works by increasing circulating levels of factor VIII and von Willebrand factor. The data available on the use of desmopressin for the treatment of bleeding in other disorders of platelet function with more complex pathophysiology (such as uraemia, recent use of antiplatelets or isolated prolongation of bleeding time) are less convincing. Desmopressin appears to reduce bleeding time in healthy aspirin-treated volunteers and in those individuals with an isolated prolonged bleeding time [19]. A meta-analysis of 10 trials (596 patients) of desmopressin in patients with platelet dysfunction (antiplatelet use or cardiopulmonary bypass) reported reduction in transfusion rates, blood loss and re-operation rates compared with placebo [20]. However, half of the included studies were conducted >20 years ago and all were in patients undergoing cardiac surgery, which carries specific risk factors for platelet dysfunction [20]. An older meta-analysis of 16 studies (1215 patients) in cardiac surgery suggested that the use of desmopressin versus placebo more than doubles the risk of perioperative myocardial infarction, without any significant benefit on transfusion rate, further operations relating to bleeding or mortality [21]. Desmopressin is relatively contraindicated in patients with cardiovascular disease, prevalent amongst patients with kidney disease, because of the reported risk of acute thrombosis (resulting in ischaemic stroke and myocardial infarction) [22].

There are limited and contradictory data regarding the use of desmopressin for renal biopsy specifically. In a single-centre, randomized, double-blind, placebo-controlled trial in 162 patients, desmopressin significantly reduced haematoma size, but there was no change in haemoglobin level in either group. Similarly, no patient in this study experienced visible haematuria, or required blood transfusion, radiological or surgical intervention [23]. All included patients in this study were considered low risk, in that they had preserved renal function (glomerular filtration rate >60 mL/min and creatinine <150 μmol/L), controlled blood pressure and normal coagulation parameters. In a retrospective analysis of a multi-centre registry of native renal biopsies in patients with creatinine >150 μmol/L, those who received desmopressin had substantially fewer major and minor complications than those who did not [24]. However, relatively

few biopsies were conducted across these centres (20/year in the centre that administered desmopressin; 37/year total across the remaining six centres). Variation in practice and operator skill mix may also account for higher rates of complications in centres that did not administer desmopressin [5].

Despite the lack of convincing evidence of benefit, and potential risk of harm, desmopressin is still used in some centres at the discretion of the responsible physician, and often in reaction to prolonged bleeding time: the time taken for bleeding to stop after infliction of a small skin wound. Measurement of bleeding time may be influenced by numerous factors that are difficult to standardize, including technical variables, use of concomitant medications and comorbidities [25]. The result is that neither normal nor abnormal bleeding times have been found to be reliable in predicting major bleeding associated with invasive procedures [25]. Similarly, bleeding time is not a reliable method of identifying patients with platelet dysfunction in association with recent aspirin/antiplatelet use [25]. As such, bleeding time is not recommended for routine assessment of bleeding risk in advance of major procedures including surgery [25–27]. By extension, there is no evidence for routine correction of abnormal bleeding time with desmopressin.

Aspirin

A systematic review of bleeding complications in patients undergoing renal biopsy on aspirin reports on four clinical guidelines and two non-randomized studies [4, 28–32]. Kumar *et al.* conclude that it is reasonable to withhold aspirin for 7–10 days in advance of renal biopsy because of lack of prospective evidence that biopsy on aspirin is safe [32]. There are a few problems with this proposition. First, stipulating that aspirin must be discontinued necessarily delays biopsy and definitive treatment. Second, and most importantly, there are no prospective controlled trials describing the broader outcomes after renal biopsy in those advised to stop aspirin, particularly relating to thrombotic complications and cardiovascular events.

Cardiovascular disease affects two-thirds of older persons with CKD [33, 34]—the majority with atherosclerotic heart disease—and accounts for 39% of deaths in patients on dialysis [34] and at least 22% of deaths in those with a kidney transplant [33]. Around 30% of adults aged over 40 years in the US report taking low-dose aspirin for primary or secondary prevention of cardiovascular disease [35]. In a major study of over 600 000 patients using low-dose aspirin for primary or secondary cardiovascular disease prevention, discontinuation of aspirin was associated with immediate and substantial (37%) increased risk of cardiovascular events, equivalent to one additional cardiovascular event per year for every 74 patients who stop aspirin [36]. The risk of aspirin cessation is further supported by a meta-analysis of aspirin discontinuation or non-adherence in patients at risk for coronary heart disease. Biondi-Zoccai *et al.* [37] describe 3-fold increase in major adverse thrombotic events (including acute myocardial infarction, stroke, other thrombosis, death) in patients who have discontinued aspirin, with average time to event of 10.7 days (95% CI 10.3–11.1). An earlier meta-analysis by Burger *et al.* [38] suggests this time interval could be even shorter for acute coronary syndrome alone (8.5 ± 3.6 days).

International consensus guidelines support ongoing use of aspirin for transbronchial lung biopsy [39]. In a prospective study to determine risk of bleeding with aspirin use in 1217 patients undergoing transbronchial lung biopsy, there was a similar rate of procedure-related bleeding compared with renal biopsy [40], but no increased risk of mild, moderate or severe bleeding in those 285 patients (23.4%) who took low-dose aspirin within 24 h of the procedure [40]. Similarly, Atwell *et al.* [31] describe data on 15 181 percutaneous core biopsies of any organ taken between 2002 and 2006, with a similar rate of bleeding in patients taking aspirin (within 10 days of biopsy) compared with those who did not (0.6 versus 0.4%, $P = 0.34$). Amongst 5832 patients in this cohort undergoing renal biopsy, there was no association between aspirin use and risk of bleeding ($P = 0.53$). In our own unit, we previously compared the rate of bleeding complications in our two centres before they merged in 2007 [4]. Routine practice in one centre was to stop aspirin 5 days before renal biopsy; aspirin was routinely continued in the other. There was no difference in the rate of major bleeding (need for transfusion or surgical/radiological intervention), and our standard practice has been to continue low-dose aspirin for renal biopsy, without increase in our rate of bleeding complications [3].

CONCLUSIONS

There have been significant improvements in practice over the past decades with regards percutaneous renal biopsy. Across centres, we appear now to have reached agreement on many aspects of this procedure, such as the need for blood pressure control, avoidance of coagulopathy, use of spring-loaded needles under direct imaging guidance and a need to monitor for complications. Whittier *et al.* and Korbet *et al.* provide reassurance that renal biopsy in the modern era remains a safe procedure with low rate of significant bleeding, albeit reporting findings from a single centre. The observed complication rate differs between centres according to variation in practice and in the definition of major complications, but the event rate of major complication is so low that either a single centre case series over a prolonged period (as in these articles) or a registry collecting data from a large area are required. We have chosen the latter, and have developed a national Renal Biopsy Registry and publish the outcomes as part of our annual renal registry report [41]. There remain areas of divergence in practice that may have unintended and deleterious consequences: administration of desmopressin and discontinuation of aspirin, for example, both carry a risk of thrombosis. It is our opinion that it is time to reach consensus on our interpretation of the available data and to draw up guidelines to standardize our biopsy practice internationally.

CONFLICT OF INTEREST STATEMENT

None declared.

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