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Abnormal coagulation tests before kidney biopsies—what next?

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Abstract

Introduction. Bleeding is one of the most feared risks from a renal biopsy. To determine this risk, a clotting screen is performed prior to the biopsy to identify any coagulation abnormalities. In addition, concerns exist with respect to bleeding from platelet dysfunction and the special cases of paraprotenemia.

Method. Literature search of all the relevant articles in relation to bleeding risk from clotting abnormalities and platelet dysfunction in the setting of kidney biopsy was conducted.

Results. Bleeding risk from abnormal clotting screen is minimal in the absence of prior bleeding history in patients with renal disease. Administration of fresh frozen plasma in these cases is probably unnecessary and often causes delay in the procedure. In a similar way, platelet transfusions may not be appropriate in those with platelet dysfunction.

Conclusions. Global coagulation function tests are now available which need to be considered to determine bleeding risk before kidney biopsy, in conjunction with a good patient history.

Keywords: coagulation; bleeding; kidney; biopsy

Introduction

Clotting screens are requested before interventional procedures like kidney biopsy to determine the risk of bleeding. This usually includes prothrombin time (PT) and activated partial thromboplastin time (APTT). Abnormalities in these screening tests often result in the delay of these procedures due to the fear of risk of retroperitoneal bleeding from the biopsy. This is despite the fact that prolongation of PT and APTT by itself has never been able to predict bleeding in any clinical circumstance [1]. However, a detailed evaluation of such a scenario has not yet been undertaken in the setting of renal biopsies.

What are PT and APTT?

In the early part of the 20th century, several attempts were made to identify the reasons for blood clotting in individuals with haemophilia [2]. Armand Quick investigated bleeding patients with obstructive jaundice and haemophilia and 'discovered' the PT. Interestingly, the PT was normal in persons with haemophilia. Further research done at the University of North Carolina led to the development of APTT, which is prolonged in haemophilia. Further elaborate research identified deficiencies of different coagulation factors in patients with bleeding disorders and abnormal clotting screens. This led to the development of the coagulation cascade incorporating several clotting factors. Recently, this system has been revamped to incorporate the important role played by platelets and other factors in the 'cell-based' model of coagulation [3]. In summary, the PT and APTT were created to identify the cause of bleeding tendency in patients who may have haemophilia or rare bleeding disorders. They were not devised to determine the risk of bleeding in persons who may require interventional procedures but are not known to have inherited disorders of haemostasis.

What causes prolonged PT and APTT?

In both PT and APTT, the sample collected from the patient into a citrated tube is made to clot with the addition of calcium and a commercial reagent which initiate clotting. In this artificial system, there are many variables which can cause test abnormalities, starting from variables in the patient (difficult venepuncture or samples obtained from access lines), and problems with the transport of the specimen (transport across hospital sites can cause exposure to heat and sometimes delay in analysis) [4].

In the otherwise ideal setting, a prolonged clotting screen reflects the reduction of one or more coagulation factors in the plasma, due to various reasons including inherited bleeding disorders, liver disease, the use of anticoagulant drugs and vitamin K deficiency. Another important reason for these abnormal results is the presence of an inhibitor in the plasma which blocks the clotting process *in vitro*. The latter is mainly due to a lupus anticoagulant and very rarely due to an antibody developing against factor VIII and other coagulation factors. It is important to note that bleeding can occur in the absence of abnormal PT and APTT (Table 1).

Table 1. Causes of prolonged PT and APTT[a]

PT[b]	APTT	Condition
Long	N	Common: vitamin K deficiency, liver disease Rare: factor VII deficiency
N	Long	Common: antiphospholipid antibody, heparin, liver disease Rare: factors VIII, IX, XI, XII deficiency, von Willebrand's disease Extremely rare: inhibitors to the above factors, high molecular weight kininogen or Prekallikrein deficiency
Long	Long	Common: vitamin K deficiency, oral anticoagulants, liver disease Rare: fibrinogen deficiency Extremely rare: factors V, VII, X and II deficiency
N	N	Common: surgical/procedure-related bleed, vascular abnormalities, platelet dysfunction Rare: dysfibrinogenaemia Extremely rare: factor XIII deficiency

[a]N, normal. The fourth row gives the clinical situations where bleeding is seen despite normal PT and APTT.
[b]PT is sometimes replaced by International Normalised Ratio (INR). Ideally, INR should only be measured in patients taking oral anticoagulants like warfarin.

What happens in the laboratory if the PT and APTT are abnormal?

If the clotting screen is abnormal, one of the first things which may be done in the laboratory is to investigate where the abnormality is in the clotting cascade. A simple guide to this is given in Table 1. The initial step is to perform a mixing study (Figure 1). This involves mixing one part of the patient plasma with one part of the normal plasma, which is known to contain normal amounts of coagulation factors. If the PT or APTT corrects to within normal range, it denotes a deficiency of coagulation factor, since the normal plasma provided the deficient clotting factors and corrected the tests. However, if after the mixing, the clotting tests remain abnormal, it suggests the presence of an inhibitor in the plasma which blocks the clotting process. This is commonly a lupus anticoagulant, an *in vitro* phenomenon, which is very common in the nephrology setting. Many kidney diseases which can lead to end-stage renal failure have been linked to the lupus anticoagulant and the anticardiolipin antibodies, which are most commonly associated with thrombosis and not bleeding [5].

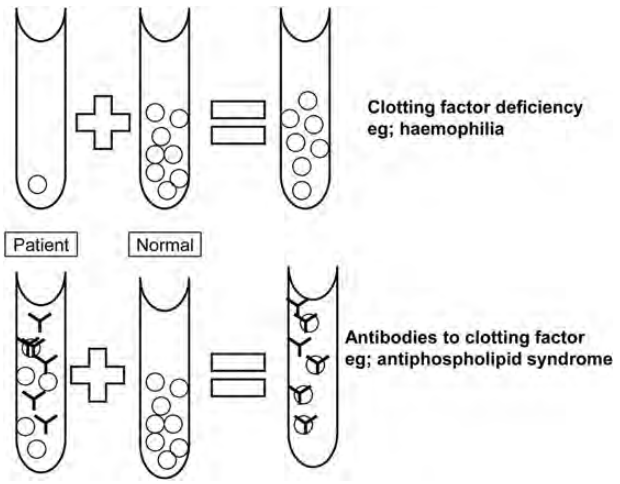

Fig. 1. The MIXING study. In the top part of the figure, plasma from a patient with low coagulation factors is mixed with a control sample with adequate (normal) coagulation factors. The result is normalization of a prolonged clotting screen. In the lower part of the figure, plasma from a patient with antibodies to coagulation factors is mixed with that from a normal control. Since the antibodies are still present in the mixed sample, the clotting screen continues to be abnormal after the mixing study. The antibodies are commonly due to a lupus anticoagulant and rarely due to acquired haemophilia.

What is the relevance of the clotting screen in renal patients?

The need for determining the patients who may bleed from a procedure like renal biopsy is only intuitive. However, what is often forgotten in this scenario is the lack of correlation between abnormal coagulation tests and bleeding risk which has been investigated in many clinical settings. First, the systematic review by Segal and Dzik, which examined 25 studies including one randomized controlled trial and 24 observation studies, demonstrated no increased bleeding risk from abnormal coagulation tests [1]. Interestingly, the bleeding tendency was similar in patients who had normal and abnormal coagulation screens suggesting the futility of these tests. This systematic review, however, only included two studies of renal biopsies, one where the transjugular route was used and another where percutaneous biopsies were done [6, 7]. In the first study, two major bleeding complications were observed in 25 high-risk patients with contraindications to percutaneous renal biopsy [6]. Both of these cases had multiple risk factors for bleeding. In the second but earlier study, the ability of coagulation assays to predict biopsy-related bleeding was specifically evaluated in 120 renal transplant patients undergoing allograft biopsy [7]. A limitation of this study was that most patients of the control group were on aspirin. Of the 21% of patients who showed evidence of 'mild' bleeding, 78% had normal results on all coagulation tests. The outcome of the study was that most mild bleeding was not associated with coagulation abnormalities. Thus, although coagulation tests are not related with bleeding events in non-renal patients (which is also shown in these two reports), systematic analyses are still awaited in nephrology patients to draw a firm conclusion.

Second, the example from the liver disease setting shows that despite moderate-to-severe prolongation of the PT and APTT, many of these patients do not bleed, as it happens with haemophilia, apart from variceal haemorrhage [8]. Tests that were planned to measure the amount of thrombin generated in patients with cirrhosis demonstrated comparable levels to normal controls [9]. This would translate to normal clot formation in cirrhotic individuals despite prolonged clotting screens. In support of this, there is a trend among the hepatologists to prescribe thromboprophylaxis in many of their inpatients who are, in contrast, at increased risk of thrombosis despite prolonged clotting screens [10].

Third, it has never been shown in the nephrology setting that patients are at an increased risk of bleeding from the coagulation factors point of view although platelet dysfunction is an important risk factor which is not studied using PT and APTT [11]. At the same time, patients with renal impairment are more at risk of thrombosis, which is not in keeping with the coagulation screen abnormality, similar to the patients with liver impairment.

Lastly, PT and APTT are very sensitive to the decrease in coagulation factors, which does not directly translate into bleeding risk. The minimum haemostatic level for most coagulation factors is ~30% or less [12]. Bleeding risk theoretically increases when the plasma content of any of the coagulation factors drops below this level. Although in the setting of a single clotting factor deficiency like haemophilia, this is relevant, in the multiple factor deficiency, the commonest situation encountered in clinical practice, PT and APTT prolongation can occur when the coagulation factor levels are considerably higher than this and most often well within the haemostatic range of ≥30% [12].

What about fresh frozen plasma for abnormal coagulation?

The general advice for administering fresh frozen plasma for abnormal coagulation stems from the fact that plasma is a storehouse of all coagulation factors including fibrinogen. However, there is no standardization of the amount of coagulation factors in plasma apart from factor VIII. In many patients with inflammatory states (chronic kidney disease being one of them), the factor VIII level tends to be high, anyway. On the contrary, studies related to warfarin reversal has shown that the factor IX (nine) content of plasma is not adequate to replace the deficient clotting factor unless large amounts are given which can be an issue in the volume-overloaded renal patients [13].

The dose of 15–20 mL/kg, which is often the suggested dose for an abnormal coagulation test, is based on the principle that 1 mL/kg of plasma raises the clotting factor levels by 1% and ~15–20% is necessary for haemostasis. This would mean that, in practical terms, administering any amount <750 mL is unlikely to be effective in any adult who weighs at least 50 kg. Since each bag of frozen plasma is around 250 mL, the not so uncommon request for two bags prior to a procedure is worthless.

The effect of plasma replacement also depends on the starting level of coagulation factors. If the levels are very low (corresponds to very prolonged PT and APTT), the plasma replacement may result in significant improvement compared with those in whom the levels are mildly decreased, where the correction of clotting screens is likely to be minimal [12]. The recent study by Stanworth *et al*. has clearly shown that the median change in International Normalised Ratio (INR) was <0.2 when it was <1.7 before plasma was transfused and 0.3 when the starting INR was between 1.8 and 1.9 [14]. This would suggest that at least with mild prolongation of clotting screens, administration of fresh frozen plasma is unlikely to contribute in any significant manner to the improvement of the clinical situation.

What about platelet dysfunction?

Bleeding is common in uraemic patients from dysfunctional platelets. Although the exact mechanism for this abnormal haemostasis is not yet known, uraemic bleeding is considered multi-factorial [15]. The different contributors to this platelet dysfunction include abnormal binding to the von Willebrand factor, platelet membrane abnormalities, uraemic toxins including guanidinosuccinic and phenolic acids, which inhibit platelet aggregation, and increased prostacyclin and nitric oxide levels which are strong anti-platelet aggregating agents [15–17]. In addition, anaemia can also worsen bleeding in uraemic patients. This is due to the deficiency of platelet aggregators, adenosine diphosphate and thromboxane, present inside the red cells and also due to abnormal rheology, wherein platelets drift to the middle of the vasculature due to the relative absence of red cells occupying the central aspect of the vessel lumen [15]. Livio *et al*. reported in the 1980s about the beneficial effect of blood transfusions in reducing uraemic bleeding [18]. Improvement of anaemia in these circumstances can reduce bleeding by allowing margination of platelets and thus, reducing platelet-related haemostatic dysfunction. In support of the benefit of correction of anaemia in the reduction of bleeding are the beneficial effects of erythropoietin on haemostasis.

Patients with platelet dysfunction secondary to uraemia typically present with mucosal bleeding unlike those with coagulation factor deficiencies. These include purpura or ecchymosis, epistaxis, bleeding from venipuncture sites and occasionally gastrointestinal or intracranial bleeding. The several methods for diagnosing platelet dysfunction include bleeding time, platelet aggregometry, platelet function analysers (PFA-100) and newer point of care tests including Multiplate analyser, Platelet Works and TEG Platelet Mapping system [19]. Although these methods have been used mainly in the setting of diagnosis of inherited platelet disorders and identifying bleeding risk in cardiology patients, detailed trials are yet to be performed in nephrology patients [20]. For this reason, a recent review summarized the current practice as 'uraemic bleeding is still based on clinical symptoms of bleeding, evaluation of bleeding time is the most useful test to assess clinical bleeding in uraemic patients' [15]. It is necessary to note that a normal bleeding time may be observed in patients with von Willebrand's disease, and aspirin users and still cause post-procedure bleeding. In a surgical setting, but not in a renal biopsy context, most specialists have now done away with bleeding time, but recent studies in the nephrology setting still used this test as the gold standard in those who may have platelet dysfunction [21–24].

Management of patients with platelet dysfunction is dependent on the urgency of the kidney biopsy [15]. If deemed urgent, desmopressin is probably the best treatment. It works by increasing the release of the von Willebrand factor from the endothelium allowing more platelet binding. It needs to be borne in mind that the dose used for uraemic bleeding is about 10-fold higher than doses used for diabetes insipidus (0.3 μg/kg intravenously or subcutaneously). In less urgent cases (>2 week window), conjugated estrogens or erythropoietin may be used. Adequate dialysis has also been shown to improve platelet dysfunction.

What about platelet transfusions?

Platelet transfusions are not necessary in uraemic bleeding tendency when desmopressin can correct the abnormal haemostasis. A different situation exists when it comes to thrombocytopaenia which may accompany cases of renal vasculitis or thrombotic microangiopathy. Platelet transfusions are often considered in these cases

with a transfusion trigger or platelet count $<50 \times 10^9$/L. This is based purely on expert opinion rather than on evidence. An interesting concept in this setting is that the lower platelet count in both renal vasculitis and thrombotic microangiopathy is due to increased platelet aggregation which should put the patient at risk of thrombosis rather than bleeding. Once again, in the hepatology circles, a compensatory increase in the von Willebrand factor has been noted in patients with thrombocytopaenia, diminishing the risk of bleeding in these patients from a low platelet count [25]. The same has not been studied in renal patients, although a contributory factor for the increased arterial and venous thrombotic risk in these patients has been suggested to be increased von Willebrand factor multimers [26].

Should antiplatelet therapy make a difference?

An increasing number of patients who require renal biopsy are on antiplatelet agents like aspirin or clopidogrel. For fear of bleeding, many nephrologists advise their patients to discontinue antiplatelet agents a week before an elective biopsy. Recent studies have, however, demonstrated an increased risk of thrombotic events with discontinuation of antiplatelet agents, even for a short time [27]. Mackinnon *et al*. addressed this very issue in a large retrospective study which compared 1120 ultrasound-guided biopsies in the two renal units, one where the antiplatelet agents were stopped 5 days prior to the biopsy while in the other, this was continued [24]. Although the risk of minor bleeding, defined as a drop in haemoglobin <1 g/dL, was higher in the antiplatelet cohort, there was no difference in the rate of major complications. A retrospective study including over 15 000 subjects (5800 kidney biopsies) who underwent percutaneous biopsies showed that recent aspirin therapy does not appear to significantly increase the risk of bleeding complications [28]. Since clopidogrel (and newer agents like prasugrel or ticagrelor) have a stronger antiplatelet function, it is advisable to withhold these agents for 5–7 days before an elective kidney biopsy. In an emergency situation, platelet transfusions can 'overcome' the platelet-inhibitory function of these drugs [29].

The unique situation of paraproteinaemia and bleeding

It has long been considered that disorders that lead to paraproteinaemia (monoclonal gammopathy of uncertain significance, multiple myeloma, Waldenstroms macroglobulinaemia and amyloidosis) are associated with an increased risk of bleeding [30]. Although bone marrow involvement in these cases leads to thrombocytopaenia, the associated problems like vascular infiltration and hyperviscosity in addition to uraemia have also been suggested to contribute [31]. Acquired platelet dysfunction is often a constant feature and may be related to uraemia or coating of the platelets by the paraproteins. In addition, specific and rare coagulation problems like abnormalities in fibrin polymerization, factor X deficiency, heparin-like circulating anticoagulants, and inhibitors to coagulation factors and von Willebrand factor are unique to these disorders and may lead to haemorrhagic complications [32].

Recent studies, however, have challenged this theoretical risk of bleeding with paraprotein disorders. Fish *et al*. analysed retrospectively 148 patients with a known monoclonal gammopathy who underwent native and transplant biopsies compared with those without paraproteinaemia and found similar rates of haemorrhagic complications (4.1% versus 3.9%) [33]. Another study from the Mayo Clinic focussed on over 100 patients with amyloidosis [34]. Post-biopsy bleeding was observed in 9.9% of patients with amyloidosis compared with 10.6% of controls although major bleeding was slightly more common in the amyloidosis cohort (4% versus 2.1%). Neither of these studies have specifically looked at the role of coagulation abnormalities or platelet problems in predicting the risk of bleeding.

What is required in the current setting for renal patients?

In simple terms, more research is required to understand the bleeding tendency in patients with renal impairment. Many tests of global coagulation screen have recently come on the scene which have suggested the potential for predicting bleeding tendency taking into account the different components of the haemostatic system, including the platelets, fibrinogen and the clotting factors. These have not been extensively studied in the renal setting, but should be considered in well-planned multicentre trials which are probably the best way forward. As in cases of liver disease, thrombin generation tests are useful to identify whether the renal patients generate the same amount of clotting despite the prolonged PT and APTT. The current practice also needs to be audited to see how the administration of plasma components in those who have abnormal clotting screens may normalize these tests. Until then, we will continue to administer plasma for coagulation tests based on very little evidence, but with possible harm to the patients. A sensible but logical approach in these cases is to go back to the

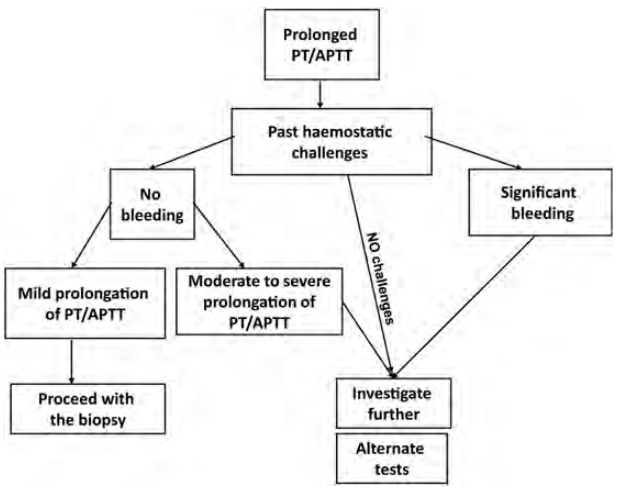

Fig. 2. Algorithm for the management of a prolonged PT and APTT. Past haemostatic challenges are dental extractions (especially wisdom teeth) or surgical procedures. In those who have had no challenges, further tests should be encouraged before biopsy. Mild prolongation of PT and APTT is 1.5 times normal. Alternate tests include thrombin generation or thromboelastography methods.

basics of medical teaching—taking a good history. At least in an older adult, who may have had haemostatic challenges in the form of surgeries like appendicectomy or tonsillectomy or tooth extractions, the absence of unexpected bleeding in any of these situations is probably the best clotting test that could have been done to determine the risk of bleeding [34]. In those with mild prolongation of clotting screens (PT and APTT <1.5 times normal) with no bleeding history, further investigations and fresh frozen plasma infusions are not necessary, in the hands of an experienced operator (Figure 2). In cases of moderate-to-severe abnormalities in coagulation tests, further tests should be considered before proceeding with renal biopsy, given its possible morbidity. Newer modalities of assessing coagulation like thromboelastogram studies may be helpful in these circumstances. Urgent collaborative trials are necessary so that we can do away with the myth that 'an abnormal coagulation test always means bleeding' in renal patients.

Conflict of interest statement. None declared.

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