Review Article

Percutaneous native kidney biopsy in patients receiving antiplatelet agents- Is it necessary to stop them routinely?

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ABSTRACT

Percutaneous renal biopsy plays an important role in the investigational approach of the nephrologist. Though the technique and the safety of the procedure has improved over the last two decades it remains an invasive procedure and can be associated with bleeding complications. To minimize the risk of bleeding, it has been the practice of many centers and nephrologists to advise patients receiving antiplatelet agents to discontinue them 5–7 days before planned procedure. This advice is based on opinion and pre-established procedure or norms rather than sound evidence based guidelines. This article aims to be a critical appraisal of this unnecessary and sometimes not so safe practice of routine stoppage of antiplatelet agents prior to kidney biopsy.

Key words: Antiplatelet agents, aspirin, bleeding, renal biopsy

Introduction

Percutaneous renal biopsy plays an important role in the investigational approach of the nephrologist. The procedure has significantly improved safety-wise over the last two decades after the routine use of spring-loaded needles and the use of real-time ultrasound guidance. However, it still remains an invasive procedure and is associated with a risk of minor/major bleeding complications. These complications may vary from center to center. Nephrologists are routinely seeing patients who are on antiplatelet agents who may present with a glomerular disease but may be vary of doing renal biopsy in such cases due to the increased risk of serious bleeding complications. To minimize the risk of bleeding, it has been the practice of many centers and nephrologists to advise patients on antiplatelet agents to routinely discontinue them 5–7 days before planned procedure. In patients who take these drugs for cardiovascular prevention or secondary prophylaxis, discontinuation of antiplatelet agents even for a short time may significantly increase the risk of thrombotic vascular events with sometimes fatal consequences. Most guidelines pertaining to the use of anti-thrombotics in non-nephrology literature recommend that antiplatelet agents can be continued throughout most surgical procedures except when bleeding might occur in a closed space such as the intracranial space. This article aims to be a critical appraisal of the practice of stopping of antiplatelet agents prior to kidney biopsy.

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Platelet Function and Antiplatelet Agents

Platelets circulate in a resting inactive state in intact blood vessels, but interact very rapidly and selectively with exposed subendothelial surfaces and altered endothelial cells.[1] The first interaction between platelets and the exposed subendothelial surface is mediated by von Willebrand factor (vWF), a high molecular weight multimer protein synthesized and released by endothelial cells but also released by circulating platelets. vWF binds to one side of subendothelial collagen via its A3 domain and on the other side to platelet GP 1b/9, thus slowing down platelet movement. Following this platelet collagen receptors GP 1a/2b come into contact with subendothelial collagen leading to complete arrest of platelets in the damaged vessel wall and their activation. Platelet activation releases cyclooxygenase-1 (COX-1), thromboxane A2 (TxA2) and other prostaglandins,

leading to the activation of the intrinsic pathway of coagulation and the formation of intravascular thrombin. Platelet degranulation and the release of platelet ADP, serotonin and matrix mellatoproteinase also contribute. This last decade has seen immense progress in the field of antiplatelet agents with newer agents being more selective in their action. However the knowledge about safety of these agents is limited in patients with renal failure with most large trials excluding patients with CKD-stage 3 and beyond. Antiplatelet agents are classified into three categories: Acetyl salicyclic acid (aspirin), thienopyridines and platelet (GP) 2b/3a receptor antagonists. The GP receptor antagonists are used to treat immediate vascular thrombosis and are hence not relevant to this discussion.

Aspirin

Aspirin was the first and is still the most widely used antiplatelet drug. Aspirin achieves a complete and irreversible blockage of platelet COX-1 at the usual dosage of 50–150 mg/day. This irreversibly inhibits platelets by reducing/inhibiting TxA2 generation, thereby reducing the formation of the platelet plug and preventing fibrin clot formation. The half-life of aspirin is 7–10 days[2] and platelet thromboxane generation is irreversibly inhibited during this period making them inactive. Although there are commercially available methods for measuring the antiplatelet effect of aspirin, none of them have actually been shown to predict the risk of bleeding after surgery or invasive procedures.[3] A daily dosage beyond 150 mg for a normal adult increases hemorraghic risk without increasing protective value. Aspirin is routinely prescribed either alone or in combination with clopidogrel for secondary prevention of cardiovascular events. In secondary prevention aspirin decreases the myocardial reinfarction rate by 30% and subsequent stroke by 25%.[4]

Thienopyridines

Clopidogrel is a platelet ADP–receptor antagonist with a half-life of clopidogrel that is short (4 h), however recovery from the effects of the drug can be 7 days or longer due to irreversible platelet inhibition.[5] Bleeding time increases to a maximum of 1.5–3 fold normal after 3–7 days of treatment. As for aspirin, normalization of coagulation relies on the release of new platelets into the circulation and not on the disappearance of the drug from the plasma. Clopidogrel acts synergistically with aspirin and has been used in combination in high-risk patients. The combination also is useful in some patients like elderly diabetic females who may demonstrate resistance to one drug. However, combination therapy substantially increases bleeding risk.

Use of aspirin is frequently interrupted before surgery/interventions to lower the risk of bleeding. But is this practice substantiated by hard evidence? Aspirin use has been associated with an increased risk of bleeding, increasing morbidity and mortality only after neurological surgery, although no increased risk has been seen in patients undergoing other major/minor surgeries.[6] Multiple studies have shown the safety of aspirin during procedures such as peritoneal dialysis catheter insertions and removal,[7] transrectal prostatic biopsies[8,9] and dental extractions,[10] percutaneous dilational tracheostomy[11] with no increased risk of bleeding. A meta-analysis of patients taking aspirin found that the risk of moderate to severe post-operative complications was doubled, although this increase translated only to an increased absolute risk of 2%.[12] Most guidelines pertaining to the use of anti-thrombotics also recommend that antiplatelet agents can be continued throughout most surgical procedures except when bleeding might occur in a closed space such as the intracranial space. A recent narrative review by Finkel *et al*.[13] states that most noncardiac surgeries can be safely performed in patients taking clopidogrel. The American Urological Association and the International Consultation in Urological Disease in their consensus statement came to the conclusion that the risk of significant bleeding complications is low for patients who require to continue aspirin for ureteroscopy, laser prostatectomy, percutaneous renal biopsies and transrectal prostate biopsies.[14]

Looking at all the available data in the nonrenal population, can aspirin be continued safely in patients undergoing native kidney biopsy, especially in patients who take them for secondary cardiovascular prophylaxis? A percutaneous renal biopsy is an essential tool for the diagnosis of primary and secondary renal disease and despite the fact that it is an invasive procedure, it has been documented to be relatively safe. Retrospective analysis of the safety of ultrasound-guided percutaneous renal biopsy done in 1090 biopsies demonstrated a frequency of minor hematoma in 2.2% of patients with no significant decrease in hemoglobin and self-limited microhematuria in 0.8% with 9% of patients having hemodynamically insignificant AV fistulae on Doppler.[15] A more recent single center study by Korbet *et al*. of 1055 real-time ultrasound guided renal biopsies done using a 14 gauge biopsy needle noted minor complications in 8.1% and major complications in 6.6% of patients.[16] Baseline features predictive of a complication were systolic blood pressure >170 mm of Hg, bleeding time >7.5 min and serum creatinine >3.5 mg/dl. Both these studies however, did not have patients on antiplatelet agents before biopsy. Another study by Manno *et al*.[17] did not

find any correlation between bleeding time and the frequency and severity of post biopsy bleeding though increased partial thromboplastin time had a correlation. The only study done in patients undergoing renal biopsy was the retrospective study by Mackinnon *et al*.[18] which compared major bleeding complications in patients continuing on aspirin versus patients in whom it was discontinued 5 days before biopsy. It was found that stopping antiplatelet agents before biopsy was associated with a lower rate of minor complications but there was no difference in the rate of major complications. The risk of bleeding while taking dual antiplatelet agents such as aspirin and clopidogrel is however more significant and though there are no adequate data to support this, clopidogrel has often been discontinued and aspirin alone continued preoperatively before major surgery.

On the other hand, the risks of stopping aspirin especially in patients taking it for secondary prevention are real and defined. Patients with coronary stents who take aspirin alone or in combination with clopidogrel, who stopped antiplatelet therapy for noncardiac surgery face a 45% complication rate and a mortality rate of 20% with the highest risk for those who had a stent placed within the previous 35 days.[19] The mean delay between patients with coronary artery disease (with or without stents) stopping aspirin and having acute coronary syndrome was only 10 days.[6,19,20] Even temporary interruption of antiplatelet agents has been found to triple the risk of ischemic stroke or transient ischemic attack.[21] Given the safety record of aspirin and the risks associated with temporary discontinuation, many authorities recommend to continuing medications during most surgeries. Patients taking aspirin for primary prevention may be able to stop the medication safely without any untoward consequences. However it is important that aspirin be continued in patients who take antiplatelet agents for cardiovascular protection. In these patients at higher risk of bleeding, the nephrologist needs to take a call on whether percutaneous renal biopsy can be done at all in these group of patients or an open/laparoscopic procedure is recommended with substantial increase in hospitalization and costs. Use of desmopressin 0.3 mc kg compared to placebo before renal biopsy has been found to significantly decrease the risk post biopsy bleeding (13.7% vs. 30.5%placebo)[22] and needs to be evaluated further. A recent preclinical testing of a novel biopsy device called therapeutic injection system (TIS) done in porcine models significantly reduced blood loss by injecting a hemostatic plug at the time of biopsy[23] and may be an option for such high risk patients in the future. It is therefore necessary that good controlled studies that can reliably predict the risk of bleeding in patients taking antiplatelet agents are needed to answer this question.

Conclusion

It may be safe to assume that with available evidence that routine discontinuation of the antiplatelet agents may not be necessary in low risk patients undergoing percutaneous renal biopsies. The nephrologist is the best person to decide this risk on a case by case assessment. The risk of inadvertent thrombotic complications needs to be balanced against the risk of major bleeding and individualized decision-making therefore is the need of the hour.

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