Management of perioperative bleeding in renal patients

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Patients with chronic kidney disease (CKD) often require surgery (vascular accesses, peripheral vascular disease, coronary disease, etc.). The surgical risk in such patients, in the same way as in the general population, depends on the type of surgery involved and on the elective or emergency nature of the operation. However, although the surgical risk is similar to that found in the general population, morbidity-mortality among renal patients is much greater than in the general population.[1]

Recently, a classification of CKD has been established involving 5 stages according to the degree of glomerular filtration (GF).[2] The aim of this classification is to allow the early identification of patients with renal disease, and to implement treatment measures destined to slow progression and/or to ensure that patients requiring dialysis can receive such treatment under good conditions. Renal patients that may require surgery and therefore are at a high risk of bleeding comprise individuals with CKD (both in predialysis and among those receiving kidney replacement therapy), patients with acute renal failure, and renal transplant patients presenting chronic graft nephropathy.

The association between bleeding and uremia has been well established for years.[3] Although the underlying physiopathology is not fully clear, a number of factors are accepted to be involved: platelet dysfunction, anemia and drugs that interfere with platelet aggregation and clotting.[4]

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Under physiological conditions, the platelets circulate within the bloodstream in an inactive form. Damage to the vascular wall activates the platelets, with the purpose of generating a provisional thrombus and securing hemostasia.

Such platelet activation comprises several phases: Once vascular endothelial damage has occurred, the platelets adhere to the subendothelium via von Willebrand factor (fvW). The adhered platelets are activated, and release the contents of their granules: ADP, serotonin. Posteriorly, via platelet surface receptor IIb/IIIa, and through the mediation of adhesion proteins (fvW and fibrinogen), the platelets aggregate among each other and with those already adhered to the subendothelium[5,6] (see fig. 1).

Patients with uremia present an acquired platelet defect that accounts for the high risk of bleeding in nephropathic patients.[7] In addition, other factors such as anemia and drugs (antiplatelet agents, anticoagulants, etc.) contribute to this acquired platelet defect.

PLATELET DYSFUNCTION

Patients with nephropathy present defects in all the mechanisms implicated in platelet or provisional thrombus formation.[4]

Adhesion defects: Although in uremic patients the levels of fvW are normal or slightly elevated, the activity of this factor is diminished[8] —thereby complicating platelet adhesion to the subendothelium.[9] In addition, it has been seen that uremic patients have increased levels of prostacyclin[10] and nitric oxide (NO)[11]— both of which are potent inhibitors of platelet adhesion.

Defects in granule content release: An acquired defect is observed in the platelet granule contents, resulting in defective release of ADP, serotonin and thromboxane A2.[12,13] Calcium in turn is necessary for platelet activation, and these patients present alterations in intracellular calcium mobility.[14]

Aggregation defects: Defects have been identified in the activity of the IIb/IIIa surface receptors.[15] The accumulation of certain substances such as urea, creatinine, phenols, and guanidosuccinic acid have been related to defects in platelet aggregation. The fact that uremic patients subjected to dialysis subsequently showed improved binding of fibrinogen to the IIb/IIIa platelet surface receptor has been attributed to the presence in the plasma of renal patients of an unidentified platelet inhibiting factor.[4]

ANEMIA

One of the main factors contributing to the appearance of anemia in CKD is a deficient production of erythropoietin (EPO), associated to the drop in GF. Other factors such as aluminum toxicity, infections or inflammatory processes can also contribute to the appearance of anemia.[16] Rheological studies have shown that the red blood cells travel through the bloodstream in the center of the vascular lumen —radially displacing the platelets, which therefore find it easier to adhere to the endothelium. A reduction in red cell mass implies that the platelets circulate more dispersedly, thereby complicating their adhesion to the vascular wall and formation of the platelet thrombus.[17]

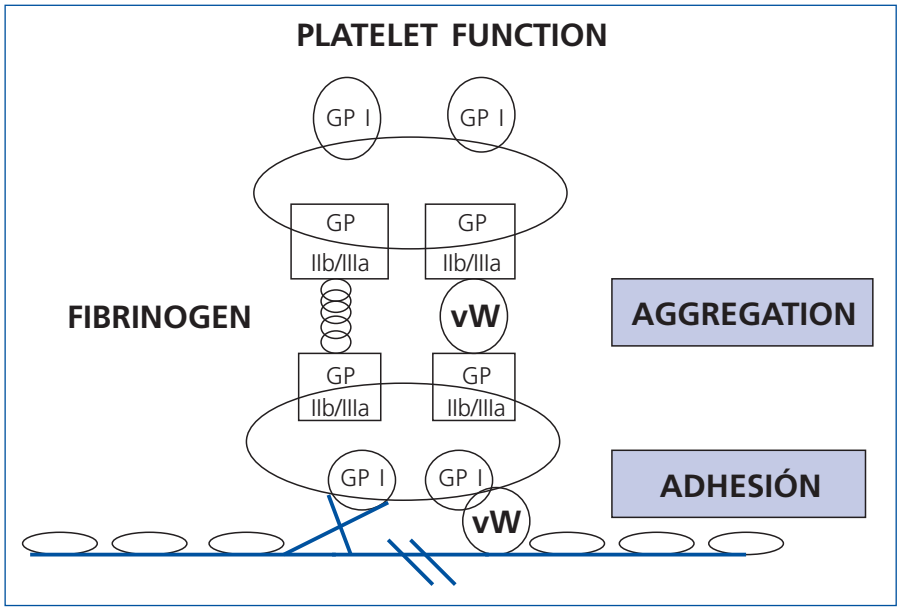

Figure 1. Platelet function under normal conditions.

ANTIPLATELET DRUGS

The use of these drugs in renal patients implies a prolongation of bleeding time with respect to the general population.[18] Glycoprotein (GP) IIb/IIIa inhibitors prevent binding of the adhesion proteins to the platelet surface receptors, as a result of which platelet aggregation is inhibited.[19] Among the GP IIb/IIIa inhibitors, abciximab, a monoclonal antibody with a short half-life (10-30 minutes), requires no dose adjustment in renal failure, since the platelet-abciximab complex is mainly eliminated via the splenic route. In contrast, other GP IIb/IIIa inhibitors such as tirofiban or eptifibatide require dose adjustments in patients with advanced CKD.

ANTICOAGULANT DRUGS

Heparin is needed in these patients, due to their important co-morbidity and the risk of thrombotic events; in such individuals, bleeding and thrombosis may coincide.

Unfractionated heparin is a heterogeneous mixture of glycosaminoglycans with molecular weights in the range of 3,000-30,000 Da. Low molecular weight heparin (LMWH) is composed of fragments of unfractionated heparin with a molecular weight of about 5,000 Da. Both types of heparin exert their anticoagulant effects by binding to and activating antithrombin III, accelerating interaction between the latter and factor Xa and thrombin —which is inactivated as a result. Unfractionated heparin is generally administered via the intravenous route for systemic anticoagulation, and is monitored by means of the activated partial thromboplastin time (aPTT). LMWH in turn is generally administered subcutaneously.[19] Due to the fundamentally renal clearance of LMWH, recent editorials and reviews recommend unfractionated heparin anticoagulation in patients with serum creatinine levels of over 2 mg/dl, or with creatinine clearance < 30 ml/min.[20,21] In those cases where the use of LMWH is decided in renal patients, it is advisable to reduce the dose 50%, and to administer a single daily dose, with monitorization of anti-Xa factor.[19]

OTHER DRUGS

Beta-lactam antibiotics (penicillins, cephalosporins, etc.) also have been related to prolonged bleeding time as a result of alterations in the platelet membrane.[22] In turn, nonsteroidal antiinflammatory drugs (NSAIDs) cause platelet dysfunction through reversible cyclooxygenase (COX) inhibition.[23]

CLINICAL MANIFESTATIONS

Patients with kidney disease are more susceptible to bleeding in the context of surgery or invasive procedures.[17] Gastrointestinal bleeding has been described as the most common bleeding complication in patients subjected to dialysis (esophagitis, gastritis, duodenitis, etc.).[4] Cerebrovascular hemorrhage in turn is more common than in the general population. A Japanese study reported an incidence of 637 cases per 100,000 inhabitants and year – this representing a 5-fold greater incidence than in the general population,[24] with a greater presence in younger patients, and a poorer prognosis than in the general population. Retroperitoneal hematomas (spontaneous or secondary to venous catheter placement) also deserve mention in patients with kidney disease.[17]

DIAGNOSTIC TESTS

There is currently no effective screening test for platelet dysfunction. Neither bleeding time nor PFA-100 (platelet function analyzer, a prototype of a new generation of analyzers designed to screen platelet function defects) is sufficiently sensitive to detect platelet defects in asymptomatic individuals. Bleeding time is dependent upon the type of incision made, the characteristics of the skin, and patient cooperation —while PFA-100 can yield prolonged readings in patients with low hematocrit values and normal platelet function. In a study of 148 patients with known platelet alterations, bleeding time sensitivity was found to be 36%, *versus* 30% for PFA-100. The combined sensitivity was 48%.[25]

PREVENTION AND PERIOPERATIVE TREATMENT OF UREMIC BLEEDING

Considering that a range of factors intervene in the physiopathology of uremic bleeding, each of them must be addressed when preventive and treatment measures are contemplated. For increased simplicity, these measures can be classified as general and specific:

a) *General measures:*

1. *Eliminate uremic toxins:* The toxins accumulated in the context of uremia contribute to platelet dysfunction. Their treatment by means of kidney replace-

ment therapy contributes to improve platelet function and shorten bleeding time.[4] Both hemodialysis and peritoneal dialysis are equally effective in clearing toxins, and thus in preventing perioperative bleeding. In the case of patients with advanced CKD who require programmed surgery, dialysis may be started before surgery is performed. In the case of patients enrolled in a hemodialysis program, dialysis is to be performed before the operation.[1,26] In order to prevent bleeding, hemodialysis is to be performed without heparin, and with frequent flushing of the system. If hemodialysis has been performed with heparin, it is advisable to wait a prudent period of time before moving the patient to the operating room.[17]

2. *Correction of anemia:* The use of human recombinant EPO and derived analogs helps improve anemia associated with chronic renal failure.[16,27] Its use requires the availability of adequate iron deposits; in this sense, the administration of oral or intravenous iron may prove necessary.[1] With these measures it is possible to correct anemia associated to CKD, and shorten bleeding time. A period of 2-6 weeks may be needed from the time of administration of EPO to the obtainment of an adequate response in hematocrit level. The use of such agents therefore should be started early, before the patient is moved to the operating room.[27] Blood transfusions are not recommended on a chronic basis, since immunization may result in patients who in future may require a kidney transplant.[28] Blood transfusions are indicated in cases of acute bleeding and emergency surgery.[1]

3. *Withdrawal of medication (antiplatelet and anticoagulant drugs):* The suspension of antiplatelet drugs should be individualized according to the type of surgery involved, with due evaluation of the risk/benefit ratio associated with suspension (i.e., thrombosis/bleeding).[29] In general, antiplatelet medication should be suspended at least 72 hours before the operation.[1] Likewise, the suspension of oral anticoagulation is advised, with the introduction of heparin, and avoiding the use of drugs commonly used in surgical services, such as NSAIDs —which reversibly inhibit COX and thus entail an increased bleeding risk.[4]

b) *Specific measures:*

1. *Desmopressin:* Desmopressin is a synthetic derivative of vasopressin-ADH, with a comparatively lesser pressor effect. Its mechanism of action in the prevention and treatment of uremic bleeding is related to the release of factor VIII and fvW multimers from the endothelium. Desmopressin is administered at a dose of 0.3 mg/kg i.v./s.c in 15-30 minutes. The time to onset of activity is 30-60 minutes, with a duration of 6-12 hours. As a result, the main indication of desmopressin is the prevention and treatment of acute bleeding, and as treatment prior to invasive procedures such as biopsies.[17,30] In a recent review of recommendations based on evidence for the management of uremic bleeding, the use of desmopressin was included with grade I recommendation and evidence A, with avoidance of the administration of a second dose (tachyphylaxis).[31]

2. *Cryoprecipitates:* Upon thawing frozen plasma, the supernatant was found to contain fibrinogen, fibronectin, factor VII and factor VIII. The use of these cryoprecipitates shortens bleeding time in uremic patients. The underlying mechanism of action is based on the provision of these factors. Administration consists of 10 U via the intravenous route, and the effect is noted within one hour, with a duration of 12-24 hours. The fact that cryoprecipitates constitute a potential source of infection has limited their use to those cases refractory to desmopressin and with frequent blood transfusions.[17,32]

3. *Estrogens:* The observation that patients with von Willebrand disease and hereditary telangiectasia improved during pregnancy led to the use of estrogens for the prevention of bleeding. The underlying mechanism of action in the prevention of bleeding is not fully clear. L-arginine (a precursor of nitric oxide) is believed to be inhibited, thereby improving platelet aggregation. Most studies involving estrogens for the prevention of uremic bleeding have used the intravenous route (0.6 mg/kg/day), though use has also been made of the oral (50 mg/day) or transdermal route (50-100 mg twice a week). The effect appears after 24 hours, with a peak after 5-7 days, and persists for two weeks. This slower onset of action causes estrogen to be used mainly for elective and chronic preparation prior to surgery.[17,29,33]

4. *Antifibrinolytic agents:* The systemic inflammation present in uremia is associated with activation of the fibrinolytic system. As a result, the use of such agents (tranexamic acid) could shorten bleeding time in uremia.[34]

The management of perioperative bleeding in uremic patients can be summarized as follows:

1. Minor surgery, tooth extractions, biopsies and emergency surgery: general measures + desmopressin.
2. Programmed major surgery: general measures + conjugated estrogens 5 days before the operation + desmopressin one hour before surgery.

In conclusion:

Patients with chronic kidney disease requiring surgery are at a high risk of bleeding, due to multiple factors (platelet dysfunction, anemia, drugs, etc.). Knowledge of these factors and the adoption of a multifactor approach to deal with each of them will allow safe surgery —reducing the high risk of bleeding in these subjects.

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KEY CONCEPTS

1. The association between bleeding and uremia is well established, and is influenced by a range of factors (adquired platelet dysfunction, anemia, drugs, etc.).

2. Deficiente von Willebrand factor activity, the absence of platelet granule contents (ADP, serotonin) and the accumulation of certain uremic toxins are the main factors responsible for platelet dysfunction in uremic patients.

3. Each of these factors must be addressed when preventive and perioperative treatment measures are contemplated.

4. The clearance of uremic toxins by dialysis, the correction of anemia, and the suspension of anticoagulants and antiplatelet drugs are the general measures required for preventing uremic bleeding.

5. Desmopressin (as a single dose) is the therapeutic agent of choice for preventing and treating acute bleeding. Cryoprecipitates are reserved for refractory acute bleeding episodes. Estrogens are indicated for the chronic prevention of bleeding.

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