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ÜBERSICHT

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Hemostasis in renal failure

Hämostase bei Nierenversagen

Zusammenfassung Eine Blutungsneigung ist seit langem als häufige und potentiell schwerwiegende Komplikation des akuten und chronischen Nierenversagens unterschiedlicher Ätiologie bekannt. An der Entstehung der hämorrhagischen Diathese bei chronischer Urämie sind sowohl vaskuläre als auch thrombozytäre Störungen beteiligt, wobei die gestörte Interaktion von Thrombozyten und Gefäßepithel eine besondere Rolle spielt. Hämodialyse und moderne Behandlungsstrategie des Nierenversagens haben das Auftreten schwerer Blutungen bei Patienten mit chronischer Urämie erheblich reduziert; gegenwärtig bestehen die hauptsächlichen Manifestationen einer abnormen Blutung in Ekchymosen, Epistaxis, gelegentlich gastrointestinaler Blutung, Hämatoperikard, subduralem Hämatom. Blutungen können nach wie vor als schwere Komplikationen nach Operationen oder Biopsien auftreten. Diese Übersichtsarbeit analysiert zunächst die Ursachen urämisch bedingter Blutungen und diskutiert sodann die Möglichkeiten einer therapeutischen Intervention.

Schlüsselwörter Urämie – Hämostase – Blutungskomplikationen – Thrombozytenfunktionsstörungen – NO – Therapie

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Summary Abnormal bleeding has long been recognized as a common and potentially serious complication of acute and chronic renal failure of different etiologies. Both vascular and platelet abnormalities seem to concur to the bleeding diathesis in chronic uremia. Dialysis and the modern management of renal failure have considerably reduced the occurrence of severe hemorrhages in patients with chronic uremia; at present the major bleeding manifestations consist in ecchymoses, epistaxis, and, only occasionally, gastrointestinal bleeding, hemopericardium, or subdural hematoma. Bleeding can still occur as a severe complication following surgery or biopsy. This review will first analyze the causes of uremic bleeding and will then discuss the therapeutic intervention.

Key words Uremia – Hemostasis – Bleeding complications – Platelet function disorders – NO – Therapeutic strategies

Introduction

The association between bleeding diathesis and acute and chronic renal failure of different etiologies has long been recognized [8, 56]. The pathophysiology of the hemorrhagic tendency in this population is thought to be multifactorial and is attributable to abnormalities of primary hemostasis, in particular platelet dysfunction and impaired platelet/vessel wall interaction.

The introduction of dialysis and the modern management of renal failure have definitively reduced the incidence of severe hemorrhages. Ecchymoses and epistaxis are the major bleeding manifestations seen today, with gastrointestinal bleeding, hemopericardium, or subdural hematoma occurring only occasionally [99]. Nevertheless, bleeding remains a potentially dangerous complication particularly in the case of trauma or surgical or invasive procedures.

Table 1 Causes of uremic bleeding

Platelet abnormalities
Subnormal dense granule content
Reduction in intracellular ADP and serotonin
Impaired release of the platelet α-granule protein and β-thromboglobulin
Enhanced intracellular cAMP
Abnormal mobilization of platelet Ca^{2+}
Abnormal platelet arachidonic acid metabolism
Abnormal ex vivo platelet aggregation in response to different stimuli
Defective cyclooxygenase activity
Abnormality of the activation-dependent binding activity of GP IIb-IIIa
Uremic toxins, especially parathyroid hormone
Abnormal platelet-vessel wall interactions
Abnormal platelet adhesion
Increased formation of vascular PGI_2
Altered von Willebrand factor
Anemia
Altered blood rheology
Erythropoietin deficiency
Abnormal production of nitric oxide

Causes of uremic bleeding

The pathogenesis of uremic bleeding is multifactorial, and involves platelet and endothelial dysfunction (Table 1). Impaired platelet-platelet and platelet-vessel wall interactions result in a prolonged bleeding time, still the best predictor of clinical bleeding [34, 40, 87]. It depends on the platelet number and function, vascular integrity, and hematocrit and, thus, gives an excellent overall assessment of primary hemostasis [40].

The platelet count in uremia is usually normal [17, 42], but platelet function is impaired. Among acquired platelet dysfunctions, low levels of intracellular serotonin and adenosine diphosphate [14, 16], high levels of intracellular cyclic adenosine monophosphate [96], a defective cyclooxygenase activity [69], and an abnormal mobilization of Ca^{++} [97] in response to stimulation play a major role in the pathogenesis of uremic bleeding.

Several abnormalities of platelet-platelet interaction have also been reported in uremia. They include defective platelet aggregation in vitro in response to various stimuli [14, 66, 68, 104] and defective platelet thromboxane A_2 production in response to endogenous and exogenous stimuli [69, 86], not correctable by thrombin [69].

Fibrinogen, von Willebrand factor (vWF) and their receptors, glycoprotein (Gp) Ib and GpIIb-IIIa complex, play a vital role in normal hemostasis, by initiating and mediating the formation of platelet thrombi at sites of vascular injury [82]. In uremia the number of GpIIb-IIIa receptors expressed on the platelet membrane is normal, but their activation is impaired: in contrast, the vWF-binding activity of GpIb is normal. Removal of substances present in uremic plasma markedly improved the GpIIb-IIIa defect, suggesting that dialyzable toxic substances are probably a major component of the altered platelet function in uremia.

The evidence that several dialyzable "toxins" (e.g., urea, creatinine, phenol, phenolic acids, parathyroid hormone or guanidinosuccinic acid) may be involved in the genesis of the uremic platelet dysfunction is not compelling [30, 67, 71]. Reducing the blood levels of these compounds, the abnormal hemostasis of patients with renal failure is partially corrected. However, no correlation has been found between bleeding time or platelet adhesion and the serum level of the dialyzable metabolites that mainly accumulate in uremia [71].

Platelet adherence to foreign surfaces is significantly impaired in uremia [36, 65, 70], but this does not fully explain the prolonged bleeding time [17, 71]. Formation of vascular prostacyclin (PGI_2), a potent vasodilator and inhibitor of platelet function, is increased in both uremic patients [70, 74] and rats with experimental uremia [38, 105]. Plasma of uremic patients contains higher than normal amounts of a factor that stimulates vascular PGI_2 [10]. This could be PTH, in view of findings that PTH increases urinary excretion of the PGI_2 metabolite, 6-keto-prostaglandin F_{1a} [79].

Quantitative and qualitative abnormalities of the vWF molecule, which promotes platelet adhesion and aggregation to subendothelial collagen [78], have also been reported. They may alter the platelet-vessel wall interaction and contribute to the hemorrhagic tendency of uremia [23]. Kazatchkine and colleagues [33] reported elevated vWF antigen levels but reduced ristocetin cofactor activity in uremic patients. However, other investigators have reported increased vWF functional activity [27, 72, 98].

The observation that cryoprecipitate [32], a plasma derivative rich in factor VIII and vWF, and desmopressin [51], a synthetic derivative of antidiuretic hormone that releases autologous vWF from storage sites, significantly shorten the bleeding time of uremic patients suggests that a functional defect in the vWF platelet interaction may indeed play a role in the abnormal hemostasis of these patients.

Platelet adhesion and aggregation in flowing systems [80, 92] are markedly potentiated by red blood cells. Red blood cells enhance platelet function by releasing ADP [20] by inactivating PGI_2 [101] and by increasing platelet-vessel wall contact by displacing platelets away from the axial flow and toward the vessel wall [92]. Several studies have extensively investigated the independent role of anemia in the bleeding tendency of uremia, demonstrating that partial correction of anemia was sufficient to correct defective primary hemostasis in uremia.

However, the newest experimental and clinical data would rather support the possibility that the bleeding tendency in uremia is associated with excessive formation of nitric oxide (NO) [73], a potent vasoactive molecule [31].

Table 2 Therapeutic strategies for uremic bleeding

Treatment	Indication	Dosage	Effect		
			Start	Peak	End
Blood or RBC transfusion	Prophylaxis of bleeding in high risk patients with anemia	According to the severity of anemia	PCV = 28–32%		Related to RBC life-span
Recombinant human erythropoietin	Prophylaxis of bleeding in high risk patients with anemia	50–150 U/kg i.v.	PCV = 28–32%		
Cryoprecipitate*	Acute bleeding episodes	10 bags	1 hour	4–12 hours	24–36 hours
Desmopressin**	Acute bleeding episodes	0.3 µg/kg i.v.*** 0.3 µg/kg s.c. 3.0 µg/kg intranasal	1 hour	2–4 hours	6–8 hours
Conjugated estrogens	Major surgery or when long-lasting effect is required	0.6 mg/kg/day i.v. infusion for 5 consecutive days	6 hours	5–7 days	21–30 days

* Use not recommended, because not uniformely observed favorable effect. ** It loses efficacy when repeatedly administered. *** Added to 50 ml saline and infused over 30 min

Plasma concentrations of the stable NO metabolites, nitrites and nitrates, were higher than normal in uremic rat with prolonged bleeding time [2]. By immunoperoxidase, higher expression of two isoenzymes responsible for the synthesis of NO, endothelial constitutive NO synthase and inducible NO synthase have been found in the endothelium of large vessels of uremic rats [2]. These results were taken to indicate that in experimental uremia there is an excessive formation of NO at systemic level, and this phenomenon is a direct consequence of up-regulation of the gene expression of NO synthase isoenzymes in vascular endothelium. Beside its vasoactive properties, NO inhibits platelet aggregation in vitro and platelet adhesion to cultured endothelial cells [53, 55]. The in vivo counterpart of this activity is the prolongation of skin bleeding time observed in healthy volunteers given NO by inhalation [29]. Thus, it has been proposed that excessive systemic NO formation may play a role in the abnormal primary hemostasis in uremia. This possibility is supported by the observation that the prolonged bleeding time returns completely normal when uremic rats are given N-monomethyl-L-arginine, a competitive inhibitor of NO synthesis [73]. In the same model we have documented that the shortening effect of either conjugated estrogen mixture or its active component, 17β-estradiol, on bleeding time is associated with a complete normalization of plasma concentrations of NO metabolites and vascular expression of NO synthase isoenzymes, which would indicate that conjugated estrogens normalize uremic bleeding by interfering with the synthesis pathway of NO [60].

Experimental data have found confirmation in humans. Thus, in patients with chronic renal failure, defective platelet aggregation is associated with increased platelet NO synthesis [58]. In addition, plasma from chronic hemodialyzed patients, unlike normal plasma, potently induced NO synthesis in human umbilical vein endothelial cells. Exactly the same results have been recently obtained in cultured human microvascular endothelial cells exposed to uremic plasma [89]. The above findings suggested that substances accumulate in plasma of uremic patients capable of up-regulating vascular NO synthesis. The stimulatory activity of uremic plasma was attributed to cytokines such as tumor necrosis factor α (TNFα) and interleukin-1β (IL-1β) that are potent inducers of the inducible isoform of NO synthase and circulate in increased amounts in the plasma of patients with chronic renal failure either undialyzed or on maintenance hemodialysis [12, 26, 49, 64].

Therapeutic strategies

The approach to uremic bleeding must be considered in two contexts, the prevention of bleeding in patients at high risk because of invasive procedures or surgery and the treatment of patients with active bleeding. The strategy depends on the urgency of the situation, the severity of uremia, and the previous therapy employed (Table 2).

Dialysis

Hemodialysis shortens the prolonged bleeding time of uremics and partially corrects platelet and platelet-endothelial dysfunction. However, removal of uremic platelet toxins by hemodialysis is not enough to fully correct the hemostatic defects of uremia. Moreover, both hemodialysis and peritoneal dialysis can potentially produce adverse effects on hemostasis. Peritoneal dialysis has been reported to cause platelet hyper-reactivity which may be related in some cases to the development of hypoalbuminemia [85].

Hemodialysis is frequently accompanied by transient platelet activation due to interactions of platelets with both dialyzer membranes [1, 3, 11, 21, 25, 54, 75, 81] and the vascular access itself [13, 102]. Himmelfarb and coworkers [28] recently showed that dialysis patients have an accelerated platelet turnover as indicated by a marked increase in circulating immature reticulated platelets as compared to normal controls, thus, supporting the concept that platelets are chronically activated by dialytic treatment. A repetitive activation of platelets that is caused by the dialysis procedure may induce platelet refractoriness to further stimulation, thereby contributing to the clinical bleeding sometimes observed temporally related to the dialysis procedure.

It has been documented that plasma levels of the potent NO inducers TNFα and IL-1β rise during dialysis. IL-1 and TNF are generated in vivo by circulating monocytes during hemodialysis with complement-activating membranes [12, 16, 49, 64]. Intact endotoxin, endotoxin fragments or other bacterial toxins may cross the dialysis membrane and activate cytokine production in vascular cells and monocytes [28, 48, 102]. It has also been suggested that acetate-containing dialysate may be a cause of high plasma IL-1β levels in hemodialysis patients [5, 26, 37, 39, 48, 49, 64]. Apart from the triggering factor, the result of the massive release of cytokines during dialysis is an increase of NO synthesis. Thus, Yokokawa et al. showed that in a subgroup of uremic patients NO production markedly increased during hemodialysis [103]. In addition in a recent study [59] it was found that plasma collected from patients after hemodialysis with acetate stimulated NO synthesis by cultured endothelial cells more than plasma from the same patients before dialysis. Thus, the negative effects of dialysis on platelet activation and NO synthesis may indeed counterbalance its positive effects of removing uremic toxins.

In addition heparin, even in small amounts, leads to transient systemic anticoagulation that enhances the risk of serious bleeding during and for a few hours after the dialysis session.

"Regional" heparinization has been used to minimize the effects of systemic anticoagulation [24, 43, 50]. Heparin is given by constant infusion through the inlet line of dialyzer. Simultaneously, protamine sulfate is infused into the outlet part before the blood returns to the patient. Even this schedule of heparin administration, however, may be associated with a high incidence of bleeding [6]. As an alternative, frequent injections of low-dose heparin can be given during dialysis to maintain a lower and more constant level [47]. Usually, heparin at 40 to 50 IU/kg is given at the beginning of hemodialysis, followed by 60% of the initial dose after 1 and 2 hours and 30% of the initial dose after 3 hours [47]. The activated partial thromboplastin time is measured hourly and should be maintained at 1.5 to 2 times the basal value.

Patients at high risk of bleeding can use an ethylene-vinyl alcohol copolymer hollow-fiber dialysis membrane that does not require systemic anticoagulation provided blood flow is maintained at greater than 200 ml/min [90].

Low molecular weight heparin has been proposed as an alternative to unfractionated heparin in patients having chronic hemodialysis who are at high risk of bleeding [44].

Recently, dermatan sulphate has been proposed [61] as an alternative to heparin since it causes less bleeding than heparin in animal models. The lower hemorrhagic property may be due to its reduced effect on platelets [19, 76]. Short-term clinical studies have been conducted in hemodialysis for chronic renal failure, testing fixed intravenous doses of dermatan sulphate against individualized heparin regimens [35, 63, 76]. Dermatan sulphate suppressed both visible clot formation in the dialysis circuit and the generation of plasma markers of coagulation and platelet activation during the procedure [22, 35, 63, 76]. It also induced a moderate prolongation of activated partial thromboplastin time (APTT) [35, 61, 63]. These effects were related to dermatan sulphate doses and plasma concentrations, which followed linear pharmacokinetics [22, 63, 76]. Effective doses ranged from 6 to 10 mg/kg body weight per dialysis session, depending on the type of dialyser and duration of the procedure [22, 35, 62, 63, 76]. Recently a comparative short-term clinical study has been performed on ten hemodialysed patients [7]. Dermatan sulphate dose can be individually titrated to suppress clot formation during hemodialysis as efficiently as does individualized heparin. Individual titration may be facilitated by injecting approximately 60% of the total dose as a bolus and the remaining as a continuous infusion and by monitoring APTT response. These findings confirm that dermatan sulphate is a suitable alternative to heparin for anticoagulation in hemodialysis, but long term comparative trials are warranted.

Aspirin and dipyridamole analogues reduce fibrin and cellular deposition on the filter membrane but increase the risk of gastrointestinal bleeding [41, 57]. PGI_2 shows some promise as an alternative [4, 91]. Given in a continuous infusion during dialysis at a mean dose of 5 ng/kg/min, PGI_2 completely inhibited platelet aggregation without causing bleeding [91]. However, PGI_2 was associated with headache, flushing, tachycardia, and chest and abdominal pain, which required careful monitoring and a physician's supervision [88, 106]. Thus the use of PGI_2 should be limited to patients at high risk of hemorrhage.

It has been suggested that peritoneal dialysis is more effective than hemodialysis in removing uremic toxins and studies on platelet function tests show improvement, but controlled studies documenting its clinical utility are lacking.

Correction of Anemia

Anemia influences bleeding time and bleeding tendency of uremics to a major extent. A study on six uremics demonstrated for the first time that red cell transfusions shortened the bleeding time and controlled abnormal bleeding [18]. This was confirmed in a larger group of patients [45]. Relieving uremic anemia by erythropoietin (rhEPO) also improved the hemostatic defects and normalized bleeding time [93]. Therefore, correction of the anemia – either acutely by red blood cell transfusion or in the long term by the use of rhEPO – is currently a major part of the overall strategy for preventing and controlling abnormal bleeding in uremia. However uremics whose red blood cell counts were fully normalized by erythropoietin also had a higher rate of thromboembolisms than those left anemic or with only partial correction of their anemia. Therefore, it seems preferable to use lower doses of erythropoietin with a target hematocrit in the range of 28 to 33%.

Cryoprecipitate and Desmopressin

Cryoprecipitate – a plasma derivative rich in coagulation Factor VIII, vWf, fibrinogen, and fibronectin, traditionally used in the treatment of hemophilia A, von Willebrand disease, hypofibrinogenemia and dysfibrinogenemia – was used in uremics with very long bleeding times which did not improve with platelet transfusions or hemodialysis or both [32]. In six uremic patients originally treated, the infusion of ten bags of cryoprecipitate was followed by normalization or significant shortening of the bleeding time and allowed surgical procedures (in a few patients) without excessive blood loss. The effect, however, was delayed (nadir of bleeding time 4 to 6 hours postinfusion) and transient (lasting no longer than 24 to 36 hours). The mechanism of action of cryoprecipitate is not known; it did not improve platelet aggregation defects, whereas blood levels of Factor VIII and vWF, normal or high before infusion, rose. The use of cryoprecipitate carries a small risk of transmitting viral diseases including hepatitis or AIDS.

DDAVP (desmopressin, 1-deamino-8-D-arginine vasopressin), a synthetic derivative of antidiuretic hormone, was introduced in the late Seventies to control abnormal bleeding in patients with von Willebrand disease and mild hemophilia A [52]. It has little smooth muscle stimulatory activity and, by releasing vWF from endothelial stores, increases plasma vWF. DDAVP has been studied in uremics as a potentially safer alternative to cryoprecipitate. An open controlled trial showed that i.v. DDAVP at the dose of 0.4 µg/kg shortened the prolonged bleeding times of patients with chronic renal failure [100].

This was confirmed in a randomized, placebo-controlled, double-blind, crossover trial in 12 uremics with a history of abnormal bleeding and prolonged bleeding times [51] infused i.v. with DDAVP, 0.3 µg/kg, added to 50 ml saline. Bleeding times were normalized in nine patients within 1 hour of infusion, were less than 10 minutes at 2 and 4 hours, and had returned to baseline by 8 hours. While no significant changes were noted in platelet adhesion/aggregation, residual prothrombin, serum T×B2, or platelet cyclic AMP, levels of vWf in the blood rose higher than the already elevated baseline values. DDAVP was well tolerated with no changes in hematocrit and plasma osmolality. The effectiveness of DDAVP in shortening bleeding time and/or controlling the abnormal bleeding associated with invasive procedures (biopsies and major surgery) in chronic renal failure has been substantiated by additional studies in which the drug was given i.v., subcutaneously [95], or intranasally [77, 83]. Repeated infusions, which may be required with major surgery, are associated with tachyphylaxis, probably due to depletion of vWF stores in endothelial cells. Although remarkably free of serious side effects on the whole DDAVP is reported to cause a mild to moderate decrease in the platelet count. Facial flushing, mild transient headache, nausea, abdominal cramps, mild tachycardia, water retention, and hyponatremia have been observed with variable frequency. There is a single report of a patient who suffered a stroke immediately after infusion of DDAVP [9].

From the data currently available it appears that DDAVP (0.3 µg/kg either i.v. or subcutaneously, or 3 µg/kg intranasally) is useful for treating acute bleeding in uremia and preventing abnormal bleeding in connection with surgery or invasive procedures.

Conjugated Estrogens

In the first study, six uremics with bleeding tendency and prolonged bleeding time were given conjugated estrogens (orally in one patient, i.v. in the other five) for total doses of 30 to 75 mg over two to five days. Bleeding times became shorter in all patients within two to five days of starting treatment, normal in four patients, and remained normal for three to ten days after drug discontinuation.

In a subsequent placebo-controlled, double-blind, cross-over trial conjugated estrogens (0.6 mg/kg added to 50 ml of saline solution and infused i.v. over a period of 40 minutes per day for five days) were administered to six uremics with anemia and prolonged bleeding times. Bleeding time was already shortened 6 hours after the first infusion, the effect lasting as long as 14 days, or nine days after the last infusion [94]. No changes were noted in levels or multimetric structure of vWF. No serious side effects were observed. A dose-finding study showed that 0.3 mg/kg had no significant effect on bleeding time, but that the effect was clearly cumulative. The effect of a single infusion of 0.6 mg/mg disappeared within 72 hours, while marked shortening of the bleeding time was achieved and maintained for 14 days with four or five infusions 24 hours

apart [94]. Studies, using dose regimens of 0.6 mg/kg/day given intravenously for five days and 60 mg/day given orally for five days were used, confirmed the effects of oral estrogen in the control of abnormal bleeding.

There is also evidence from a small, placebo-controlled trial in four uremic patients that conjugated estrogen given orally as a dose of 50 mg daily may markedly shorten the prolonged bleeding time after an average of seven days of treatment and may be effective in controlling abnormal bleeding [84]. Besides transient hot flushes (rare), minor side effects of conjugated estrogen include nausea, vomiting, loss of libido, and gynecomastia, which may limit its prolonged use, particularly in men. The risks of malignancy and thromboembolic complications with intermittent high-dose, conjugated estrogen are unknown.

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