Minimizing Hemorrhagic Complications in Dialysis Patients

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J. Am. Soc. Nephrol. 1991; 2:961-975

ABSTRACT
Renal failure is associated with an increased incidence of hemorrhage from a variety of sites, particularly in patients undergoing surgical procedures. The primary factors in the pathogenesis of bleeding in renal failure are platelet biochemical abnormalities and alterations in platelet vessel wall interactions. Hemodialysis improves hemostatic abnormalities in uremia, but the need for heparinization during the procedure may increase the bleeding risk. The risk of bleeding may be minimized by using peritoneal dialysis or alternative means to routine heparinization to prevent clotting in the extracorporeal circulation during hemodialysis. These include use of minimal heparin, prostacyclin, regional citrate anticoagulation, and no anticoagulation. Continuous arteriovenous hemodialysis may also be performed with regional citrate anticoagulation. There are several nondialytic therapies that may be used to prevent or treat hemorrhage in renal failure patients. These include administration of cryoprecipitate, 1-deamino-8-arginine vasopressin, estrogens, red blood cells, and erythropoietin. A clinical strategy to minimize bleeding complications in dialysis patients is presented.

Key Words: Bleeding, renal failure, anticoagulation

Richard Bright first reported bleeding associated with the uremic state in 1827 (1). It is now well established that renal failure causes hemostatic abnormalities that result in an increased incidence of hemorrhagic complications. These complications are common in patients with acute renal failure as well as in those with ESRD. They vary from minor events such as ecchymoses to life-threatening complications such as pericardial tamponade, gastrointestinal hemorrhage, and intracranial bleeding. Effective hemodialysis may result in correction of the hemostatic abnormalities of uremia, but bleeding episodes are still frequent in dialed patients.

In this discussion, we will review the various bleeding problems associated with renal failure and focus on the therapeutic options to minimize hemorrhagic complications in high-risk patients.

HEMOSTATIC DEFECTS OF UREMIA

The pathogenesis of bleeding in renal failure is not completely understood but is multifactorial. We will discuss this topic briefly; the reader is referred to comprehensive reviews of this topic for further details (2,3).

The primary factors in the hemostatic abnormalities of uremia are platelet biochemical abnormalities and alterations in platelet vessel wall interactions (4). Although the platelet count in uremic patients tends to be lower than that in the normal population (5), it is generally not low enough to account for impairment of hemostasis. Studies have revealed a variety of biochemical abnormalities that may contribute to platelet dysfunction in uremia. ADP and serotonin, compounds that play an important role in platelet aggregation, have been found to be reduced in platelets of patients with renal failure (6). Increased levels of platelet cAMP described in uremia may also inhibit platelet aggregation (7). Renal failure has been found to result in abnormalities of platelet arachidonic acid metabolism. Abnormal platelet aggregation has been described in response to arachidonic acid (8). Thromboxane A2 formation has been found to be defective in response to endogenous as well as exogenous stimuli (9). This may be because of alterations in the release of arachidonic acid or to a cyclooxygenase defect.

The fact that dialysis partially corrects platelet dysfunction (10) has led to the suggestion that uremic toxins may cause platelet defects. Urea, creatinine, guanidinosuccinic acid, phenolic acid, and parathyroid hormone have been studied. High concentrations of urea have been shown to result in mild platelet ag-
ggregation defects in normal volunteers (11). Guan-
dosuccinic acid (12) and phenolic acid (13) have been
shown to alter platelet aggregation. High levels of
parathyroid hormone may adversely affect platelet
function (14). Parathyroid hormone has been shown
to inhibit platelet aggregation in response to various
stimuli (15,16). However, another study found no
correlation between secondary hyperparathyroidism
(17) and alterations in platelet aggregation. The fact
that dialysis does not normalize the bleeding time in
uremia suggests that uremic toxins are not the sole
factor contributing to the thrombocytopenia.

There are various factors which may cause altered
platelet-vessel wall interactions. One compound that
has been proposed to play a major role is prostaglan-
din I2 (PGI2), a prostaglandin with vasodilatory and
antiaggregatory properties (18). Increased PGI2 pro-
duction has been found in blood vessels from uremic
patients with prolonged bleeding times (19). There
may also be a decrease in PGI2 metabolism in uremia
(20). Alterations in factor VIII and von Willebrand
factor may be important in the bleeding tendency of
uremia (2). A recent study has shown that endothe-
lial-derived relaxing factor, nitric oxide, plays a role
in the bleeding tendency of uremia (2I). Administra-
tion of N-monomethyl-L-arginine, an inhibitor of ni-
tric oxide formation from L-arginine, normalized
bleeding time when given to uremic rats. Nitric oxide
may interfere with hemostasis by preventing the
vasoconstriction that follows vessel injury and by
inhibiting platelet adhesion to vascular endothelium.

Anemia may also play a role in altering platelet
adhesion to the endothelium. An increased red cell
concentration in blood has been demonstrated to
increase platelet adhesion to aorta in an in vitro flow
system (22). In addition, the red cell may have a role
in thrombus formation (23). Livio et al. found a sig-
nificant negative correlation between bleeding time
and packed cell volume in uremic patients (24). Pro-
longed bleeding times were reduced when uremic
patients were transfused with red blood cells to
packed cell volumes of 30%.

Thus, the uremic state is associated with a defect
in primary hemostasis. This may be compounded by
heparinization during dialysis and by the use of an-
ticoagulant therapy to maintain access patency or to
treat other medical disorders.

Hemorrhagic Pericarditis

Pericarditis occurs as two distinct clinical entities
in patients with renal failure (25-27). Pericarditis
may develop in patients with acute or chronic renal
failure before the initiation of dialysis (uremic peri-
carditis) or in patients who have been maintained on
chronic hemodialysis (dialysis-associated pericarditis).

The incidence of uremic pericarditis has declined
over the years, reflecting earlier initiation of hemodi-
alysis, and studies show an incidence of 2 to 17% (27-31).
The incidence of symptomatic dialysis-related
pericarditis has remained fairly stable at 0 to
15% (26-29). Hemorrhagic pericardial effusion may
occur as a complication of pericarditis in either of
the above settings, although it is more frequent in
dialysis-related pericarditis. The percentage of
deaths in dialysis patients due to hemorrhagic peri-
carditis is reported at 3 to 5% (32,33). It has been
suggested that heparin administration during dial-
alysis may play a role, but there is no direct evidence
available to support this theory.

There is general agreement that uremic pericarditis
is an indication for the initiation of dialysis. There is
approximately a 90% response rate to this therapy
(33); however, 15% of patients may have recurrence
of pericarditis. Dialysis-associated pericarditis re-
ponds less uniformly to intense dialysis, with resolu-
tion in less than two thirds of patients (26,34). In
many instances, surgical intervention is required
(26,34). In both types of pericarditis, a method of
avoiding systemic anticoagulation during hemodi-
alysis to minimize the risks of hemopericardium is
required.

GI Bleeding

Gastrointestinal GI bleeding occurs with greater
frequency and is associated with a higher mortality
in patients with renal failure than in the general
population (35), and upper GI hemorrhage is the sec-
ond leading cause of death in acute renal failure (36).
The bleeding diathesis of the uremic state (37), as
well as intermittent anticoagulation, may contribute
to the increased incidence of GI bleeding.

Peptic ulcers (gastric or duodenal) are the most
common cause of upper GI bleeding (38,39), but hem-
orrhagic esophagitis, gastritis, duodenitis, and gas-
tric telangectasias may also cause significant gas-
trointestinal bleeding (40-44). Autopsy studies have
found an increased prevalence of peptic ulcer disease
in dialysis patients (40), whereas endoscopic studies
have revealed that the incidence is not increased in
these patients (45).

Hemorrhagic gastritis is a common cause of GI
bleeding in patients with untreated renal failure (46).
This is less frequent in patients treated with hemo-
dialysis. In a group of 60 patients on routine hemodialysis studied by endoscopy, gastritis was found in 22%, nodular duodenitis was found in 60%, and esophagitis was found in 37% (41). Therapy with antacids to increase luminal pH has been shown to reduce the incidence of hemorrhage (47). Antacids, H2 blockers in doses adjusted for renal failure, and sucralfate have been shown to be effective in healing peptic ulcer disease (48,49).

Angiodysplasia is a small vascular lesion of the GI mucosa and submucosa which may cause acute or chronic GI hemorrhage (43). These can be located throughout the GI tract but are more often found in the upper GI tract in patients with renal failure (42–44). The most common method of diagnosis of angiodysplasia is by endoscopic observation. If a lesion is actively bleeding, it should be treated with endoscopic therapy by electrocautery, heater probe, or laser. If a patient is not found to have another source of bleeding, an angiodysplastic lesion may be assumed to be the cause of bleeding even if not actively bleeding. These lesions should be treated if the patient has had recurrent or severe bleeding (43). Ancillary studies support the use of progesterone/estrogen agents to minimize bleeding from these lesions (50,51).

When bleeding is slow, radiological assessment of the upper GI tract may be performed. When bleeding is more pronounced, rapid diagnosis with fiberoptic endoscopy of the stomach and duodenum is effective in defining the bleeding site (52).

Bleeding from the lower GI tract may also be due to a number of different etiologies. In the small intestine, uremic patients may develop enteritis with diffuse mucosal ulceration (53). This is generally reversed by adequate dialysis. Colonic hemorrhage is not uncommon in dialysis patients and may be due to colitis, ischemic disease, perforation, diverticulosis with hemorrhage, angiodysplasia, or neoplastic (40,53,54). Uremic colitis may occur in up to 10% of patients. Pseudomembranous colitis may occur in patients on dialysis or after transplantation and may be life threatening. Ischemic bowel disease may occur with increased frequency in patients with renal failure, particularly after nephrectomy or after renal transplantation (55). Diverticulosis may occur with increased frequency in dialysis patients, particularly patients with polycystic kidney disease (56). Colonic hemorrhage from diverticulitis may occur and may be localized by selective angiography. Infusion of vasopressin or injection of autologous clot or gelfoam into the bleeding vessel may be effective. If not successful, surgical removal of the affected colonic segment is indicated.

Ulcers of the colon (57) or rectum (58) may hemorrhage. These occur more commonly in transplant patients. Diagnosis is made by colonoscopy or arteriography and generally requires colonic resection.

Although anticoagulation during hemodialysis is not the cause of these conditions, it is a serious complicating factor. When GI bleeding occurs, treatment of the underlying condition is mandatory. Techniques that correct the bleeding tendencies of uremia and minimize intradialytic anticoagulation are essential.

**Intracranial Hemorrhage**

Subdural hematoma have been reported to occur into up to 3% of patients on dialysis (59) and are frequently fatal. As with other bleeding complications, subdural hematoma were reported with more frequency before the mid-1970s. Etiological factors include anticoagulation, head trauma, hypertonic dialysate which may cause brain shrinkage and shearing of vessels, brain swelling during hemodialysis, rapid ultrafiltration for fluid removal, and hypertension (60).

Subarachnoid bleeding may also occur with increased incidence in dialysis patients (61,62). It has frequently been associated with anticoagulation. The patient typically has seizures, followed by development of coma. Computed tomographic scanning can accurately define the hemorrhage, but mortality approaches 100%.

Intracranial bleeding requires either conversion to peritoneal dialysis or some method of no or regional anticoagulation with hemodialysis. The duration after hemorrhage that these techniques should be continued is unclear, but the minimal duration is probably 2 wk.

**Hemorrhagic Pleural Effusion**

The pleural effusion of renal failure may be hemorrhagic (63,64). Anticoagulation during dialysis may be a major factor in causing bleeding in patients with fibrinous pleuritis.

Patients are admitted with pleuritic chest pain. Pleural rubs are common and may be associated with pericardial rubs. Treatment includes more vigorous hemodialysis or peritoneal dialysis and pleurocentesis. The value of nonsteroidal anti-inflammatory drugs or corticosteroids is not clear (65). Decortication may be required to prevent restrictive lung defects in patients with recurrent hemorrhagic pleuritis.

**Retroperitoneal Hemorrhage**

Spontaneous retroperitoneal hemorrhage is a rare complication in patients on chronic hemodialysis (66,67). Predisposing factors include trauma and anticoagulation. The presenting symptoms and signs include sudden onset of pain in the abdomen, flank, back, or hip, with an associated drop in blood pres-
sure. Subsequently, a distended abdomen with loss of bowel sounds may develop. The hematocrit drops in the absence of any obvious blood loss.

Confirmation of retroperitoneal hemorrhage may be made by computed tomographic scanning. Adrenal function should be assessed. Treatment includes blood transfusions, discontinuation of anticoagulation, and bed rest. Surgical exploration is rarely required.

Subcapsular Liver Hematoma

Spontaneous subcapsular bleeding may occur in the liver of patients on dialysis (68,69). This should be considered in the patient with right upper quadrant pain and decreasing hematocrit without obvious blood loss. Surgical intervention may be required for evacuation and/or hepatectomy.

Ocular Hemorrhage

Subconjunctival hemorrhage occurs with increased frequency in renal failure patients (70). This may result from heparinization during dialysis, with Valsalva maneuver, or with no obvious cause. There is no visual loss, and the hemorrhage generally resolves without any therapy.

Bleeding may also occur in the anterior chamber of the eye (71). Intraocular bleeding has been found to occur in a large percentage of transplant and dialysis patients after cataract surgery. The hemorrhage was found to clear, in all instances, without permanent loss of vision.

It has been assumed that anticoagulation associated with hemodialysis would encourage retinal bleeding in diabetic patients. However, recent studies have not supported this conclusion (72,73).

When ophthalmic bleeding complications occur, it is prudent to avoid systemic anticoagulation. Minimum heparin, no heparin, or regional anticoagulation techniques are warranted.

Uterine Bleeding

Women developing ESRD usually experience irregular menses or amenorrhea. However, in many women, intermittent uterine bleeding resumes after initiation of dialysis with correction of metabolic effects of uremia. One half of patients return to a normal cycle (74). In 10% of women, excessive vaginal bleeding may develop requiring gynecological intervention.

Most women with excessive uterine bleeding respond to curretage followed by administration of exogenous steroids to replace hormone deficiency and stabilize endometrial stroma. Alternative approaches to uterine bleeding include progesterone-impregnated intrauterine devices, intracavitary insertion of radium, and at last resort, hysterectomy (75).

Surgical Bleeding

The uremic state might be expected to commonly cause hemorrhagic complications intraoperatively or perioperatively, but this is generally not a problem if hemostasis is diligently maintained. There are certain clinical situations in which this may pose a problem. Anticoagulation for dialysis will obviously affect surgery. The effect of routine doses of heparin appear to last for 4 to 6 h after dialysis. An organized strategy that includes preoperative intense dialysis, transfusion therapy, correction of any bleeding disorder, and some method of no or regional anticoagulation with dialysis is required (76,77).

THERAPEUTIC STRATEGY TO REDUCE BLEEDING COMPLICATIONS

Classification of Patients with Increased Bleeding Risk

A system for classifying risk of hemorrhage in dialysis patients was described by Swartz and Port (78) and has been employed in most subsequent studies of bleeding risk in dialysis patients.

Bleeding risks were classified as follows: (1) "very high risk," active bleeding at time of dialysis; (2) "high risk," active bleeding stopped for less than 3 days or surgery or trauma within the previous 3 days; (3) "moderate risk," active bleeding stopped for more than 3 days but less than 7 days, surgery or trauma within the previous 3 to 7 days, or uremic pericarditis or pleuritis; and (4) "low risk," greater than 7 days after active bleeding, surgery, or trauma.

Dialysis Alternatives in High-Risk Patients

Peritoneal Dialysis. In patients at increased risk of hemorrhage, peritoneal dialysis would appear to be the dialytic method of choice. Aside from the bleeding risk associated with the catheter insertion, this technique obviates the risk of further bleeding due to the administration of anticoagulants.

Peritoneal dialysis has been specifically recommended in certain situations such as patients with head trauma (79), patients with grossly contaminated peritoneal cavities (80), patients with cardiac instability, and those patients expected to be at increased risk of bleeding for prolonged periods of time.

Unfortunately, in a large number of patients, the use of peritoneal dialysis is not feasible, and the risk of peritonitis must be taken into account in each instance. Peritoneal dialysis may be contraindicated in patients with open abdominal wounds, with recent intestinal anastomoses, after surgery (such as aortic aneurysm repair) in which the peritoneal membrane
is not intact, and in hypercatabolic states. These patients frequently fall into the high bleeding risk group. Thus, the development of techniques to avoid systemic anticoagulation during hemodialysis in patients with renal failure has been necessary.

**Hemodialysis.** Routine hemodialysis requires systemic anticoagulation to prevent clotting in the extracorporeal circulation. In most patients with renal failure, this is not associated with bleeding problems. However, in patients with an increased risk of bleeding, as described in the previous section, various techniques have been described to limit bleeding complications. These include regional heparin anticoagulation with protamine reversal, minimal heparin, use of prostacyclin, regional citrate anticoagulation, and hemodialysis without anticoagulation (Table 1).

**Regional Heparinization.** The earliest method developed to reduce dialysis-related bleeding complications was regional heparinization (81–85). A constant infusion of heparin is infused into the inlet line of the dialyzer. Simultaneously, a constant infusion of protamine sulfate is infused into the outlet port before the blood returns to the patient. During dialysis, samples of blood from the patient from the dialyzer circuit (before return to the patient) are analyzed for clotting times. The infusion pumps are adjusted to keep the whole blood-activated clotting time of the patient nearly the same as baseline and that of the artificial kidney at 250 s. The protamine dosage necessary to keep the heparin neutralized can be determined by a protamine titration test (81,83), which determines the lowest protamine/heparin ratio.

Although this method has been employed for over 25 yr, the fact that bleeding complications are reported greater than by the simpler technique of minimal heparinization (78) make its disadvantages stand out: (1) An additional infusion pump and inlet port are required in the dialysis setup to permit infusion of protamine. (2) It is sometimes difficult to determine proper infusion rates of heparin to achieve extracorporeal but not systemic anticoagulation. (3) Despite a normal clotting time at the end of dialysis, systemic rebound anticoagulation may begin 2 to 4 h after completing dialysis and may last up to 10 h. This rebound is caused by the heparin-protamine complex being broken down in the reticuloendothelial system and heparin reentering the circulation (86,87). This can be minimized by attempting to limit the heparin infusion to decrease the WBACT of the return blood rather than by increasing the protamine. Decreasing the heparin infusion during the last hour of dialysis or administration of an additional small bolus of protamine 3 h after dialysis may prevent rebound anticoagulation.

In general, regional anticoagulation with heparin followed by protamine reversal has been abandoned in favor of techniques with less complexity and fewer systemic complications.

**Minimal Heparinization.** Another method commonly employed to reduce bleeding complications is the use of the minimal dose of heparin, which will maintain anticoagulation in the extracorporeal circuit (78,88–95) (Figure 1). The modeling of the heparin requirements of a patient can be helpful in achieving this goal. A pharmacokinetic model for controlled administration of heparin was first de-

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**Table 1. Results of Different Anticoagulant Techniques for Dialyzing Patients with High Bleeding Risk**

<table>
<thead>
<tr>
<th>Technique</th>
<th>No. of Dialysis Treatments</th>
<th>Bleeding Complications (%)</th>
<th>Severe Dialyzer Clotting (%)</th>
<th>Reference No.</th>
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<tbody>
<tr>
<td>Regional Heparin</td>
<td>29</td>
<td>24</td>
<td>28</td>
<td>82</td>
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<tr>
<td>Regional Heparin</td>
<td>122</td>
<td>19</td>
<td>0</td>
<td>78</td>
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<td>10</td>
<td>0</td>
<td>96</td>
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<td>0</td>
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<td>50</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Regional Citrate</td>
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<td>18</td>
<td>0</td>
<td></td>
</tr>
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<td>108</td>
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<td>111</td>
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<tr>
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<td>1</td>
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</tr>
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<td>97</td>
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<tr>
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<td>19</td>
<td></td>
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<tr>
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<td>0</td>
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</tr>
<tr>
<td>No Heparin</td>
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<td>0</td>
<td>6</td>
<td>126</td>
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Journal of the American Society of Nephrology 965
Minimizing Hemorrhagic Complications

Figure 1. Circuit diagrams for hemodialysis by (A) minimal heparin anticoagulation (91), (B) RCA (108), and (C) no heparin anticoagulation (122).

scribed by Gotch and Keen (91). This was based on a first-order kinetic model and was further developed for use in hemodialysis by Farrell et al. (92,93). The pharmacokinetic model is dependent on two parameters: the sensitivity of the patient to heparin and the first-order elimination rate constant. These values can be determined by the use of whole blood activated clotting times or thrombin clotting time whole blood activated partial thromboplastin time.

The use of heparin modeling has permitted a reduction in the empirically chosen heparin doses of 50 to 70% without causing clotting in the dialyzer and reducing the bleeding complications (93). In a carefully controlled trial, Swartz and Port demonstrated a reduction in bleeding complications from 19 to 10% by using minimal heparinization versus regional heparinization with protamine neutralization in patients at increased risk of bleeding (78).

In a study of 300 dialyses using minimal heparinization, Swartz found 16 bleeding complications (96). In the highest risk group, bleeding occurred in 26% of patients. In a subsequent study comparing minimal heparinization to the use of prostacyclin, a higher incidence of bleeding complications was noted in the patients receiving minimal heparinization during dialysis (97). Without the actual pharmacokinetic determinations, low-dose heparinization has been performed more empirically by frequent measurements of clotting times with small variations in rates of heparin infusion and/or small boluses. Doses of heparin can be reduced to ranges of 1,500 to 2,500 U with the use of minimal heparin.

The advantage of minimal heparinization is that no additional equipment or alterations in dialysate are required. With careful monitoring of the arterial limb pressure, the incidence of partial dialyzer clotting is less than 5%. The major disadvantage is that minimal heparinization may still result in systemic anticoagulation with resultant risk of bleeding.

Prostacyclin. Although heparin inhibits gross clotting of the dialyzer membranes, it may aggravate deposition of fibrin in the membrane and subsequent platelet aggregation. Prostacyclin (PGI), an arachidonic acid metabolite, is a potent inhibitor of platelet aggregation and vasodilator with an in vivo half-life of 3 to 5 min. Prostacyclin was first used by Turney et al. (98,99) to reduce the heparin requirements for hemodialysis in patients at increased risk of bleeding. Subsequently, a number of studies demonstrated that prostacyclin could replace heparin as the sole anticoagulant in acute (97,100,101) and chronic (97,98,100,102–105) hemodialysis.

Prostacyclin is generally infused at 4 ng/kg/min into the venous dialysis access before dialysis and into the dialyzer circuit between the blood pump and dialyzer during hemodialysis. The dose of prostacyclin is then lowered if the patient experiences side
effects or is increased to a maximum of 8 ng/kg/min if there is evidence of clotting in the extracorporeal circuit (97,100).

Side effects of prostacyclin infusion include headache, light-headedness, facial flushing at lower doses, and hypotension at higher doses (97,100,102,103). With low-dose prostacyclin (4 to 8 ng/kg/min), it has been possible to perform hemodialysis despite vasodilatation (97,102). Hypotension is less frequent if bicarbonate rather than acetate buffer is employed (103). A prostacyclin analog, 15-cyclopentyl-\(\omega\)-pentanor 5 (5)-6, 9 metano PG\(\text{I}_2\), free of hypotensive effects, has been used in clinical trials for dialyzer anticoagulation (106).

A recent prospective trial showed that there was a significant decrease in bleeding complications with prostacyclin compared with minimal heparinization for hemodialysis in a high-risk group (97). Although the residual dialyzer volume was lower after the use of prostacyclin, dialyzer efficiency as indicated by changes in BUN and creatinine were not significantly different between the two groups. Use of prostacyclin infusion prevents the drop in platelet count due to extracorporeal aggregation (104) and the rise in plasma free-fatty acid concentrations (105) found in hemodialysis with heparin anticoagulation.

The advantage of prostacyclin is that hemodialysis can be performed without systemic anticoagulation, and it appears to reduce the bleeding risk compared with minimal heparinization (97).

Disadvantages include expense of the agent, the potential for clotting the dialyzer, hypotension secondary to vasodilation, and the other above-mentioned side effects, which require close patient monitoring. These problems have prevented widespread use of this agent.

RCA. The use of regional citrate anticoagulation (RCA) for hemodialysis was first described by Morita et al. almost 30 yr ago (107). However, only in the last few years since the description of this technique by Pinnick et al. (108), has this technique been widely used. Anticoagulation of the hemodialysis assembly is achieved by the continuous infusion of isosmotic trisodium citrate solution (102 mM) into the blood withdrawn from the patient (Figure 1). The infusion rate is adjusted to maintain an activated clotting time of greater than 200 s (200 to 300 mL/h). Calcium free dialysate containing acetate or bicarbonate is circulated through the dialyzer, resulting in the removal of calcium by complexation with citrate and dialytic removal. Because the blood returning to the patient is calcium depleted, 5% calcium chloride is infused into the venous return line at a rate of 0.5 mL/min.

A modification of this technique was developed in which a hypertonic trisodium citrate solution (1.6 M) and conventional dialysate containing 3.0 mEq/L calcium are used (109). The citrate solution is administered by the pump normally used for heparin on the dialytic assembly. This eliminates the need for higher filtration rates, calcium free dialysate, and calcium chloride infusion.

RCA has been successfully employed in the treatment of both acute (108,110,111) and chronic (107,109,111–117) renal failure. In one controlled comparison of RCA and low-dose heparin in patients at increased risk of bleeding, the incidence of dialysis-associated bleeding was significantly more frequent in those patients receiving low-dose heparin (50%) than in those in which RCA was used (18%) (111). In a group of patients who underwent cardiorthoracic surgery, we found a reduction in sanguinous chest tube drainage during the initial postoperative dialysis (115).

The use of RCA has been shown to maintain or reduce the activated clotting time in patients during the course of dialysis (108,109). The efficiency of dialysis, as determined by changes in creatinine and urea concentrations, is comparable to that found with heparin anticoagulation (109).

The advantage of citrate anticoagulation is that systemic anticoagulation can be completely avoided. By using the hypertonic citrate technique developed by Von Brecht et al. (109), only one additional line to add the citrate is required in the extracorporeal circuit. An additional benefit is that red blood cell transfusions may be given through the arterial limb during the dialysis procedure.

Disadvantages include the need for additional equipment, increased ultrafiltration and potential risk of hypercalcemia, hypocalcemia, hypernatremia, and metabolic alkalosis due to citrate intoxication (118). When carefully monitored, the incidence of complications has been very low in large trials (110,111).

Hemodialysis Without Anticoagulation. Several groups have evaluated various techniques for hemodialysis without anticoagulation after Glaser and colleagues were successful in performing heparin-free hemodialysis in 1979 (119). The technique of hemodialysis without anticoagulation involves pretreatment of both the blood lines and the kidney with heparin-containing solution (120–126) (Figure 1). Characteristically, 2,000 to 5,000 U of heparin in a liter of saline are flushed across the kidney and the blood lines. The lines are subsequently flushed clear with normal saline so that no heparin enters the patient. Blood flows are rapidly increased to 250 to 300 mL/min and are kept at that level for the duration of the treatment. Saline flushes of 25 to 50 mL are used to minimize hemoconcentration during ultrafiltration across the artificial kidney and to wash fibrin strands from the kidney into the bubble trap. These saline flushes are usually performed every 15
min and as needed if fibrin stranding is noted in the artificial kidney. One-to-one nursing is usually required for this technique to be successful, as the arterial limb pressure must be closely monitored.

By modifications of the technique outlined above, three large clinical trials have been performed. Sanders and colleagues reviewed their retrospective experience, predominantly in patients after and before renal transplantation with hollow fiber artificial kidney and were successful in maintaining solute clearances and avoiding the need for anticoagulants (120). Schwab and coauthors performed a 1-yr prospective trial predominantly in hospitalized intensive care unit patients with acute renal failure (122). By using parallel plate kidney, they carried out greater than 92% of their treatments without needing to resort to anticoagulants. Over 50% of the patients were unstable and maintained on vasopressors during these treatments. Temporary venous catheters were used in the majority. Approximately 7% of the patients required conversion to minimal heparin because of problems with clotting in the extracorporeal circuit. Caruana and coauthors further modified these techniques for outpatient hemodialysis (123). Clotted blood lines in artificial kidneys occurred in less than 3% of the episodes, and no other significant morbidity was noted in these clinical trials. The effectiveness of no heparin hemodialysis in unstable patients with significant risk of bleeding is well established with less than 10% of the patients needing conversion to mini-dose heparin to complete their treatments (120–126).

No heparin hemodialysis has been shown to maintain urea nitrogen and phosphate clearances as well as ultrafiltration when compared with anticoagulated controls (120,122,124,125). In addition, there were no significant differences in intradialytic hypoxemia or platelet degradation rates compared with anticoagulated controls. Conventional dialysis parameters such as fibrinogen and antithrombin III levels, as well as bleeding times, PT, and PTT, were unchanged during these techniques (121–125). Most importantly, no episodes of dialysis-related bleeding were shown in any of the above trials. Recent observations from Duke University have shown no changes in clotting rates with this technique, despite the widespread use of erythropoietin resulting in higher mean hematocrit in chronic hemodialysis patients.

The advantages of no heparin hemodialysis are that no anticoagulants of any type are required. No specific hardware or specific testing procedures are required. Specific disadvantages include the need for one-to-one nursing because of close monitoring of the venous and arterial pressure alarms and careful monitoring of the artificial kidney and the bubble trap for fibrin stranding or early signs of clotting. In addition, higher blood flows (250 to 300 mL/min) are required as well as a willingness to convert to low-dose or mini-heparin therapy in approximately 4 to 5% of patients treated. An additional disadvantage is that transfusion should not be performed during these treatments via the hemodialysis circuit because of the danger of hemoconcentration.

CAVH/CAVHD. Slow continuous renal replacement therapy is being used with increasing frequency in critically ill patients with acute renal failure (127–134). The advantages of this family of therapies is continuous physiological ultrafiltration and solute removal with limited cardiovascular strain.

The technique involves the insertion of an arterial line and a venous return line. Because of the need for maximum pressure and flow, a femoral or central arterial catheter is optimal. The pressure gradient from the central arterial catheter to the venous line pushes blood through the extracorporeal circuit through a highly permeable hemofilter where ultrafiltration and solute transfer occur. The technique is termed slow, continuous ultrafiltration, if ultrafiltration is the only procedure performed. If replacement fluid is added, predilution or postdilution so that plasma water exchange is occurring, the technique is considered continuous arteriovenous hemofiltration (CAVH). In addition, if dialysate is dripped in countercurrent fashion across the hemofilter as in hemodialysis, the technique is termed continuous arteriovenous hemodialysis (CAVHD) (Figure 2). Because of the relatively slow blood flows, anticoagu-

![Figure 2. Circuit diagrams for heparin CAVHD (A) and citrate CAVHD (B). Sampling ports are marked: peripheral (a), prefiltre (b), postfilter (c), and ultrafiltrate (d) (from reference 134 with permission).]
lution across the artificial kidney and blood lines is of preeminent concern. In general, the procedure has required systemic anticoagulation with heparin, because of the relatively slow blood flows employed and the likelihood of hemoconcentration. The use of predilution infusion fluid to minimize hemoconcentration routinely allows anticoagulation intensity to be reduced (128). Regional anticoagulation with protamine reversal has been reported (132) but has similar complications to regional anticoagulation in hemodialysis and has not been widely accepted. Prostacyclin was effective as the sole anticoagulant in postdilutional hemofiltration but was associated with cardiac instability (133). In most centers, the use of predilution fluid and low-dose continual heparin anticoagulation is required for successful continuous therapy (127–131). Most centers attempt to keep activated clotting times one to one-half times normal or PT T one and one-half times normal when sampling from the postdilution port with heparin infused into the first available port in the arterial line (127–131). In most instances, it is possible to avoid complete systemic anticoagulation but anticoagulation of the extracorporeal circuit is required.

Recently, Mehta and colleagues have described RCA for CAVHD (134) (Figure 2). After using several different techniques, these authors adopted a technique that involves anticoagulation through the proximal arterial port with 4% trisodium citrate at approximately 170 mL/hr with concomitant predilution saline or replacement fluid infusion. The authors removed calcium from the dialysate because they noted that, when calcium was present, an increased dosage of citrate was needed to maintain proper anticoagulation. A central venous catheter is employed to maintain a calcium infusion to ensure adequate calcium administration to prevent hypocalcemia and prevent citrate-induced alkalosis. Several patients treated with this protocol required administration of hydrochloric acid via central venous line to correct their alkalosis. Although the method was complicated, Mehta and colleagues were able to successfully perform CAVHD without bleeding complications in the patients tested. Whether the side effects from citrate yield a substantial advantage over low-dose anticoagulation with heparin remains to be established.

Because of the low blood flow rates employed, no heparin techniques with saline flushes have been disappointing in CAVHD (134).

Nondialytic Therapy

There are several nondialytic therapies that have been employed to prevent or treat hemorrhage in patients with renal failure. These include administration of cryoprecipitate, 1-deamino-8-arginine vasopressin (DDAVP), estrogens, red blood cell transfusions, and platelet infusion (Table 2).

Cryoprecipitate. The precipitate obtained when plasma is frozen and thawed (cryoprecipitate) has been shown to be enriched in factor VIII, fibrinogen, and fibrinectin. When administered to uremic patients with prolonged bleeding time, cryoprecipitate shortened the bleeding time and reduced hemorrhage in patients who underwent surgery (135). The effect of cryoprecipitate on bleeding time was apparent 1 h after administration, maximal at 4 to 8 h, and not detectable after 24 h. Preparation of cryoprecipitate varies, and some preparations may be less effective. In addition, cryoprecipitate poses a risk of hepatitis similar to that of whole blood.

DDAVP. An alternative to cryoprecipitate is DDAVP. Infusion of this synthetic analog of antidiuretic hormone has been shown to shorten bleeding times in uremic patients with hemorrhagic tendencies and prolonged bleeding times (136,137). DDAVP induces an increase in factor VIII release from storage sites into the plasma (138). Patients with renal failure have normal to increased levels of factor VIII activity. Watson and Keogh found that only the factor VIII ristocetin activity increased significantly after DDAVP administration, and levels of factor VIII co-

<p>| TABLE 2. Alternative agents found to reduce bleeding time in uremia |</p>
<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Onset of Effect</th>
<th>Duration of Effect</th>
<th>References No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDAVP</td>
<td>0.3–0.5 μg/kg i.v.</td>
<td>1 h</td>
<td>4–24 h</td>
<td>136–137</td>
</tr>
<tr>
<td></td>
<td>0.3 μg/kg s.c.</td>
<td></td>
<td></td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>3.0 μg/kg intranasal</td>
<td></td>
<td></td>
<td>140</td>
</tr>
<tr>
<td></td>
<td>10–20 U i.v.</td>
<td></td>
<td></td>
<td>135</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>2.5–25 mg orally</td>
<td>1–4 h</td>
<td>4–24 h</td>
<td>141</td>
</tr>
<tr>
<td>Conjugated estrogen (Premarin)</td>
<td>2.5–25 mg orally</td>
<td>2–5 days</td>
<td>3–10 days after discontinuation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6 mg/kg i.v. daily</td>
<td>6 h</td>
<td>9–25 days after discontinuation</td>
<td>51,142</td>
</tr>
<tr>
<td>Estrogen-progesterone (Enovid)</td>
<td>2.5/1 or 5/0.75 mg</td>
<td></td>
<td></td>
<td>50</td>
</tr>
</tbody>
</table>
agulant activity and factor VIII related antigen activity remained unchanged [136]. It was suggested that the effect of DDAVP on bleeding times was not related to alteration of factor VIII activity but might be due to promotion of platelet aggregation.

Subsequently, Mannucci et al. showed a consistent increase in factor VIII coagulant activity, as well as factor VIII-related antigen and ristocetin cofactor [137]. There was also appearance of larger multimers of factor VIII: von Willebrand factor after infusion.

The shortening of bleeding time after i.v. infusion is apparent within 1 h and lasts for 6 to 8 h. The recommended dose for uremic patients undergoing surgery is 0.3 to 0.4 U/kg body wt in 50 mL of saline infused over a 30-min period. In a recent study, s.c. DDAVP (0.3 μg/kg) was found to be as effective as i.v. DDAVP in shortening the bleeding time in uremia [139]. The use of intranasal DDAVP, effective in von Willebrand's disease and hemophilia, has been reported to be of benefit in uremia [140].

**Estrogens.** Conjugated estrogens have also been shown to be effective in the treatment of uremic bleeding. The fact that bleeding time was improved in women with von Willebrand's disease during pregnancy led to a trial of conjugated estrogens in uremic bleeding. Daily administration of conjugated estrogen resulted in improvement or normalization of bleeding time after 2 to 9 days of therapy [141]. A subsequent controlled study showed that daily administration of conjugated estrogens for 5 days to patients on maintenance hemodialysis with bleeding tendencies resulted in a reduction in bleeding time 6 h after initial injection, reached a maximum effect in 5 to 7 days, and lasted for 14 days [142].

Preliminary studies with estrogens have shown that they may be effective in treating mucosal bleeding from GI telangiectasias, gastritis, or duodenitis (50,51).

The specific mechanisms by which estrogens reduce bleeding time in uremia are unclear; however, it may be due to inhibition of vascular prostacyclin synthesis, known to be increased in uremia. The dosage employed has been 0.6 mg/kg of conjugated estrogen infused daily for 5 days. Potential side effects of hormonal therapy include nausea and vomiting, loss of libido, gynecomastia, thromboembolic disease, and risk of malignancy. Further controlled studies are needed to show the benefits and risks of estrogen therapy in uremia.

**Red Blood Cell Transfusions and Erythropoietin.** There appears to be a correlation between low hematocrit and prolonged bleeding time in uremic patients. In vitro, it has been shown that platelet adhesion to endothelium of rabbit aorta increases as the hematocrit increases [22]. This beneficial effect of red blood cells on bleeding time has also been demonstrated in vivo by transfusion of washed red blood cells (24). The bleeding time was shortened by raising the hematocrit to 30% or above.

Thus, the hemostatic defect in severely anemic patients may benefit from red blood cell transfusions to a hematocrit of 30%. Recombinant human erythropoietin has also been found to be beneficial in reducing prolonged bleeding times in uremia by correcting anemia [143,144]. By using low-dose erythropoietin over 12 wk at a dose that only partially corrected anemia (hematocrit of 27 to 32), bleeding time was normalized in a group of uremic patients with bleeding times greater than 15 min [144].

**Platelet Transfusions.** Because of the qualitative platelet defects associated with uremia, transfusions of normal platelets have been employed for the treatment of uremic bleeding or the prevention of intraoperative and postoperative bleeding. However, it appears that normal platelets exposed to uremic plasma rapidly develop functional defects [145]. Although occasional reports have shown platelet transfusions to be of value, there is no good evidence to support their use in uremic bleeding.

**Future Directions.** Several alternative methods to prevent extracorporeal circulation clotting without systemic anticoagulation have been examined.

Low-molecular-weight heparin appears to have antithrombotic properties comparable to unfractionated heparin but causes less bleeding [146–148]. Low-molecular-weight heparin has been used in preliminary clinical studies and may prove to reduce the risk of bleeding when compared with unfractionated heparin.

Nafamstat mesilate, 5-amidino-2-naphyl p guanidinobenzoate dimethanesulfonate, is a multienzyme inhibitor which has been employed as an anticoagulant for hemodialysis [149]. This compound, like prostacyclin, undergoes rapid metabolism with a biological half-life of under 8 min. Nafamstat inhibits enzymes of the coagulation cascade, and its anticoagulant effect was shown to be primarily limited to the extracorporeal circuit.

A variation of regional anticoagulation with heparin has been studied in which enzymatic degradation of heparin by heparinase is employed before blood reinfusion (150,151). Clinical trials have not been reported.

A few studies have looked at the possibility of producing tubing and dialyzers that are less prone to thrombosis by bonding heparin or other compounds to the surface [152,153].

**CLINICAL STRATEGY FOR MINIMIZING BLEEDING COMPLICATIONS**

Preoperative and high-risk patients with uremia should have their bleeding time assessed in addition to routine measures of coagulation including PT/PTT.
and platelet count (Figure 3). Abnormal bleeding times should be corrected by the infusion of DDAVP or cryoprecipitate. Estrogen therapy is warranted if the risk of bleeding is likely to be prolonged. When possible, transfusion to a hematocrit of 30 should be performed to further minimize bleeding tendencies. In elective cases, several days of consecutive hemodialysis, not only to minimize uremic bleeding factors but also to improve fluid and acid-base balance, should be undertaken preoperatively. When dialysis is required in high-risk patients, it should routinely be performed by the no heparin technique or by one of the methods for regional anticoagulation (citrate, prostacyclin). If long-term avoidance of anticoagulation is required, such as after subarachnoid hemorrhage, conversion of these patients to peritoneal dialysis should be considered.

The development of several proven techniques (no heparin hemodialysis, RCA) has been shown to markedly reduce hemorrhagic complications. Each hospital center should have the capacity to perform one of these techniques in the group of patients at high or very high risk of bleeding. As the risk of bleeding lessens, conversion of patients at low or moderate risk of hemorrhage to minimal heparinization for anticoagulation during hemodialysis is a reasonable step. By using the above scheme, as the patient's risk of bleeding lessens, he or she may be converted to routine systemic heparin anticoagulation for hemodialysis.

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Minimizing Hemorrhagic Complications


