Severe Clotting During Extracorporeal Dialysis Procedures

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The prevention of extracorporeal clotting during hemodialysis maximizes the effectiveness of treatment by maintaining patency in the dialyzer blood compartment and thereby obviating several important consequences. For example, clotting leads directly to blood loss, as much as 200–300 ml for each episode, depending on the total volume of the extracorporeal circuit. In addition, clotting reduces dialyzer clearance and thus the adequacy of dialysis treatment. Finally, clotting increases the overall cost and complications of hemodialysis.

Prevention of clotting during extracorporeal dialysis procedures is accomplished successfully in most instances using intermittent systemic heparinization and hemodialysis sometimes can be accomplished without anticoagulation at all (1, 2). However, occasional patients manifest extreme resistance to heparin and suffer vascular access thrombosis or recurrent severe clotting of the extracorporeal circuit. Although the latter phenomenon, severe clotting of the extracorporeal circuit, is observed infrequently (3, 4), it is striking and problematic when it occurs. In evaluating possible causes and appropriate treatments for such clotting, several important factors which must be considered include: the characteristics of the extracorporeal circuit and its components, intrinsic abnormalities in circulating coagulation factors, and the effects of exogenous agents on the coagulation system.

Pathogenesis

Mechanical Reduction of Blood Flow

The most common cause of increased clotting in the extracorporeal circuit during hemodialysis is reduction in blood flow, usually the result of mechanical abnormalities in the vascular access or in the extracorporeal circuit itself (3, 4). Most often such abnormalities are easily detected, although reduced blood flow may be more subtle in settings such as continuous arterio-venous hemofiltration in which neither blood pump nor pressure and flow monitors are employed. Therefore, mechanical reduction in blood flow should always be considered when inordinate clotting has occurred during hemodialysis or related procedures.

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Interaction of Blood and Synthetic Materials

Extracorporeal circulation of blood in synthetic tubing and devices can lead to activation of circulating inflammatory mediators such as complement components and formed elements in the blood such as WBC and platelets. This activation can occur with or without heparin and is associated with platelet aggregation, reduced platelet count and fibrin accumulation on the dialyzer membranes (5–9).

These interactions are thought to depend on the adsorption of plasma proteins on the surface of the dialyzer membrane (10), and it appears that the specific type of membrane may be important. For example, cuprophane dialyzers appear to be associated with more heparin resistance and platelet consumption when compared with polyacrylonitrile, polysulfone or polymethylmalonylacetate dialyzers (9, 11–16). Furthermore, even the composition of the blood tubing may be implicated, and tubing composed of silicone rubber may be associated with platelet and fibrin accumulation in excess of that observed using other plastic materials (17).

One other physical factor sometimes thought to contribute to dialyzer clotting is low dialysate pH (18), a consideration when using sorbent or bicarbonate dialysis systems in which dialysate pH may be subphysiologic at times. Finally, there is some evidence linking higher hematocrit to both improved bleeding time and platelet function as well as extracorporeal fibrin deposition (19–21). This association of hypercoagulability with increased hematocrit may counter some of the clinical benefits of erythropoietin administration in hemodialysis patients.

Circulating Coagulation Cofactors

In addition to the extracorporeal factors and interactions with synthetic materials, there are also recognized abnormalities in several intrinsic coagulation factors which might be associated with hypercoagulability and which have been described in hemodialysis patients. First among these factors is antithrombin III (AIII), a 65 kilodalton protease inhibitor synthesized in the liver. Low levels of AIII activity may occur in patients with hereditary defects in liver synthesis of AIII, with increased AIII consumption due to extensive intravascular thrombosis or to ongoing heparin administration, and with increased urinary AIII loss in nephrotic syndrome (22–24). Familial AIII deficiency has been noted with a frequency of 1 in 2000–5000 of the general population, and most often involves a reduction below normal in circulating AIII activity of less than 30%

(22). A moderate increase in heparin resistance has been associated with a 40–60% reduction in AIII activity in familial cases, while severe resistance has been noted when AIII is reduced by more than 60% (22, 23).

Studies in dialysis patients suggest that, in general, AIII levels may be somewhat low (25–27) and that levels may fall slightly during hemodialysis (27, 28); however, the extent of these changes is small and does not ordinarily result in coagulation abnormalities. Several individual cases of severe AIII deficiency associated with severe clotting have been reported among hemodialysis patients (29). Therefore, AIII deficiency should be considered when severe extracorporeal clotting occurs, particularly when mechanical causes of reduced blood flow cannot be identified and when renal failure is associated with underlying nephrotic syndrome.

Other plasma cofactors associated with hypercoagulability include protein C, a vitamin K dependent plasma protein which can neutralize factors V and VIII, and protein S. Relatively low circulating levels of protein C in uremic patients, levels which may decrease further following hemodialysis, are thought to reflect platelet activation and thrombin generation during the dialysis procedure (30–32). Nonetheless, specific reports of hypercoagulability due to protein C or protein S deficiency among hemodialysis patients are anecdotal at best and require further confirmation (33). Other reports suggesting an additional role for protein C or protein S deficiency in the syndrome of skin necrosis with systemic calciphylaxis (34) leave open the possible pathogenetic effect of hypercoagulability in causing small vessel thrombosis among dialysis patients. If such pathogenetic mechanisms prove true, then abnormalities in protein C and protein S metabolism may well be implicated in many instances of hypercoagulability among hemodialysis patients.

Pharmacologic Agents

Circumstances arise in which pharmacologic agents appear to activate the coagulation system and result in increased clotting. For example, agents such as conjugated estrogens and DDAVP, which improve the bleeding time in uremic patients, have been associated with hypercoagulability and excessive clotting in hemodialysis patients (35, 36). In addition, erythropoietin treatment for the anemia of chronic renal failure has also been shown to improve platelet function among dialysis patients and, therefore, to be associated with possible enhancement of thrombosis (21, 37).

Heparin itself has even been associated with immunologic activation of platelets and resulting thrombocytopenia (38, 39). Furthermore, some authors feel that heparin may be responsible for the hypercoagulability associated with syndromes such as priapism in the hemodialysis setting (40). However, evidence suggests that hypercoagulability due to heparin-related platelet activation is very unusual in the general hemodialysis population (41). Finally, agents such as nitroglycerin have been reported to interfere with the anticoagulant activity of heparin and to be responsible for hypercoagulability in the non-dialysis setting (42); thus, surveillance for such phenomena in the dialysis setting is warranted.

Other Clinical Settings

Hypercoagulability has also been described in settings of striking general illness, such as septicemia, circulatory collapse, and malignancy, with or without the presence of renal failure or dialysis (43). To date no particular predisposition to hypercoagulability has been ascribed to renal failure or dialysis in these severe conditions, but it seems reasonable to expect an increased tendency toward clotting when severe illness complicates acute or chronic renal failure.

Diagnosis and Treatment

The management of extracorporeal clotting associated with hemodialysis ordinarily involves increasing the heparin dosage. However, the need to increase heparin dosage presents the clinician with a particular challenge when there is an increased risk for bleeding in a dialysis patient, since heparin will potentiate the likelihood of bleeding from any intracorporeal sites (3, 4). Therefore, because mechanical reduction of blood flow most often causes extracorporeal clotting and will not be amenable to increased heparin, it is appropriate to evaluate for extracorporeal occlusion or for correctable lesions such as stenosis of the vascular access before increasing heparin dosage.

Unusual cases in which specific cofactor abnormalities are identified may be amenable to replacement therapy. For example, treatment using synthetic AIII has been described in hemodialysis patients with low AIII activity (44). Alternatively, agents which inhibit platelet activation, particularly short-acting parenteral agents such as prostacyclin (45–47) or longer-acting agents such as sulfinpyrazone (48, 49), might be useful when hypercoagulability is associated with hyperaggregability. In some instances, the use of dialyzer membranes such as polyacrylonitrile which do not acutely activate inflammatory mediators (9, 11–16) may also prove useful in such hypercoagulable patients.

When heparin itself appears to contribute to the hypercoagulability, or when the pathogenesis is unclear, alternative methods for preventing extracorporeal clotting might prove useful. For example, low molecular weight heparinoids may avoid immunogenicity and prove more effective in some circumstances (50), although the specific use of these agents under circumstances of hypercoagulability in hemodialysis has not been reported. Another alternative to heparin use is regional anticoagulation using citrate plus calcium neutralization in hemodialysis (51) or in continuous arteriovenous hemofiltration (52). Finally, there are reports describing membrane materials which are bonded with heparin itself to retard clotting (53), or with heparinase (54) or prot-

amine (55) which removes circulating heparin at the time of blood return. However, the clinical utility of these latter materials for general use is yet to be demonstrated.

Conclusion

Unfortunately, no single predominant pathogenetic entity causing hypercoagulability has been described in the dialysis setting. Therefore, no consistently successful or clearly indicated method for treating or preventing such hypercoagulability is yet available. In the meantime, rigorous clinical surveillance for abnormalities such as those outlined here may help to define at least a subset of patients for whom both pathogenesis as well as directed therapy can be identified.

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