**BRIEF REVIEW**

**Diagnosis and Management of Disseminated Intravascular Coagulation: The Role of Heparin Therapy**

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Disseminated intravascular coagulation (DIC) is caused by a variety of underlying disorders, and criteria for diagnosis are not well defined. However, the most helpful are a low platelet count, positive plasma protamine test, and fibrinogen and fibrin degradation product levels viewed in the context of the patient's underlying disease. The cornerstone of therapy is prompt treatment of the underlying disease and elimination of the trigger mechanism. Additional treatment must be individualized, and generalizations are difficult to make. However, if the patient has low hemostatic factors and is actively bleeding or requires an invasive procedure, then replacement with the appropriate hemostatic factors should be tried. Heparin is indicated in patients with purpura fulminans and venous thromboembolism, but there is little evidence that heparin reverses organ dysfunction associated with DIC. In addition, heparin is also probably indicated in patients with retained dead fetus and hypofibrinogenemia prior to induction of labor, excessive bleeding associated with a giant hemangioma, and neoplastic disease, particularly promyelocytic leukemia. Although the use of heparin in acute forms of DIC remains controversial, the majority of studies suggest that it is not helpful. The role of antithrombin III (AT-III) concentrates is unknown, but they theoretically may be helpful when DIC is associated with very low AT-III levels, as is seen in liver disease.

Disseminated intravascular coagulation (DIC) is a dynamic pathologic process triggered by activation of the clotting cascade with resultant generation of excess thrombin within the vascular system that leads to further activation of the coagulation system, shortened survival of certain hemostatic elements, deposition of fibrin in the microcirculation, and activation of the fibrinolytic system. Lowered levels of hemostatic factors and secondary fibrinolysis may result in clinically excessive bleeding, particularly when the patient's blood vessels have been damaged by vascular punctures, trauma, or surgery. In contrast, fibrin deposition may cause micro- or macrothrombosis and occasionally results in a fragmentation-type hemolytic anemia. The primary goal of this review is to briefly discuss the diagnosis and management of this very complex problem with an emphasis on the indications for heparin therapy. Allotted space prevents me from discussing in detail the underlying disorders causing DIC and the trigger mechanisms involved. In addition, DIC in neonates and infants, which presents special problems, will not be reviewed. The reader is referred to some excellent recent reviews of these subjects.

DIC should not be considered as a disorder in itself but as a process that is caused by a great variety of underlying diseases. Therefore, the clinical and laboratory manifestations in a given patient are extremely variable and not only depend on those features due to DIC but also those due to the underlying disease. In addition, the intensity and duration of activation of blood coagulation and the rates of thrombin formation, the state of the fibrinolytic system, the rate of blood flow, and the level of function of the liver, bone marrow, and macrophage system are of crucial importance in influencing the clinical picture and laboratory findings. Thus, in some patients, DIC will be of little clinical significance and the diagnosis established from laboratory tests. In contrast, in other patients the degree of severity is such that the features of the underlying disease are obscured by the presence of excessive bleeding and/or hypoperfusion or thrombosis. Because of this great variability, it is not surprising that the criteria for the diagnosis of this disorder are not well defined. However, it is clear that the frequency of diagnosis of this disorder depends on two factors: (1) the awareness of physicians of the occurrence of DIC in certain clinical settings (e.g., the patients with gram-negative endotoxemia, gun shot wounds to the brain, etc.) and (2) the laboratory criteria that are used in a given medical center to make the diagnosis. Although there is some degree of agreement as to the occurrence of DIC in certain clinical settings, the laboratory criteria used for diagnosis are extremely arbitrary, and very few laboratory results can be analyzed without taking into account the individual patient's underlying disease and the state of various organs' function. For example, since fibrinogen
levels rise during pregnancy and as an acute phase reactant in infection, the fibrinogen levels may be "normal" in DIC, complicating these problems. Therefore, it is not surprising that fibrinogen levels have been reported to be normal in up to 57% of patients with DIC. In contrast, in DIC complicating severe liver disease, a low fibrinogen level may be due to decreased synthesis as well as increased consumption. Similar problems may arise when using other criteria in the presence of underlying diseases that affect that parameter, for example, (A) thrombocytopenia in the presence of acute leukemia, splenomegaly, or sepsis, (B) low factor V or low antithrombin III levels in the presence of liver dysfunction, (C) factor VIII levels in the presence of pregnancy or infection, and (D) elevated fibrin degradation products (fDP) in the presence of extravascular hemorrhage, serous effusions, edema, or primary fibrinogenolysis.

Because of the lack of specificity of the above criteria, some investigators feel that the laboratory diagnosis of DIC requires evidence that thrombin has cleaved the fibrinogen molecule. This reaction is demonstrated by the presence of fibrin monomer–fibrinogen complexes in the patient's plasma using either the plasma protamine or ethanol gel paracoagulation tests. However, the ethanol gel test is frequently negative in the presence of DIC, whereas the protamine test has a very high sensitivity but suffers from a low specificity. Other more recent and experimental methods that detect products that result from the direct action of thrombin on fibrinogen (fibrinopeptide A levels) or the direct action of thrombin on factor XIII (double-D-dimer degradation product) are probably too sensitive and/or not yet clinically practical. In practice, no single laboratory test can be used to confirm or exclude the diagnosis of DIC, but the combination of a low platelet count, positive plasma protamine test, fibrinogen and fDP levels viewed in the context of the patient's underlying disease, appear to be the most helpful indicators.

Because of the tremendous heterogeneity of the underlying disorders causing DIC and the great variability of the manifestations of DIC in a given patient, there has been a great deal of controversy on how to properly manage this problem. Obviously, the cornerstone of treatment is prompt and vigorous treatment of the primary cause of the DIC. Moreover, it is also clear that a good understanding of the pathophysiology and natural history of the underlying disease and trigger mechanisms involved contributes a great deal to the logical and rational management of these patients. For example, the superb clinical studies of Pritchard and Brekken, clearly elucidated the natural history of DIC secondary to abruptio placentae. Patients with this disorder almost universally have evidence of DIC, and because of the concealed blood loss, a significant degree of hypovolemia. Serial studies in these patients clearly delineated that DIC ends with evacuation of the uterus, and the patients only have significant bleeding when their fibrinogen levels are less than 150 mg/dl. These observations led to the rational management of this disorder with blood volume replacement, prompt delivery, and cryoprecipitate when indicated. Similarly, serial prospective blood clotting studies in patients with gun shot wounds to the brain have clearly shown that in most patients the DIC is self-limited and has usually ended by the time the patient has arrived at the hospital. Therefore, rational management of these patients is to replace fibrinogen with cryoprecipitate and to correct thrombocytopenia with platelet concentrates.

Following the identification of the cause of the DIC and prompt institution of appropriate specific and aggressive supportive therapy for the underlying disease, there are several questions that must be asked to determine whether replacement of depleted hemostatic factors is necessary and interruption of DIC with heparin is to be seriously considered.

1. Does the Patient Have a Low Fibrinogen Level, Low Platelet Count, and/or Low Clotting Factor Level? If so, is the Patient Actively Bleeding?

If the answer to the second question is no, and the patient does not require surgery, then replacement therapy is probably unnecessary. In contrast, if the patient is actively bleeding and/or requires a surgical procedure, it probably will be necessary to attempt to replace the appropriate hemostatic factors, which usually means replacement with cryoprecipitate, fresh frozen plasma, and platelet concentrates. The argument that replacement therapy may "fuel the fire" and cause thrombosis in patients with active DIC is theoretically possible, but only on occasion has been proven to occur. However, it is clear that replacement therapy is most effective in those patients with very low levels of platelets and fibrinogen in whom DIC is self-limited and/or concluded, e.g., in a gun shot wound to the brain before debridement. Another problem that is encountered frequently is the failure to effect a rise in the level of hemostatic factors when the patient is bleeding with active DIC. In these cases it may be necessary to replace the hemostatic factors while under the "cover" of a continuous heparin infusion. The apparent paradox of administering anticoagulants to a patient with a serious bleeding disorder has
been emphasized repeatedly, but on occasion it may be necessary.

2. Does the Patient Have Evidence of Fibrin Deposition Such as Dermal Necrosis in Purpura Fulminans, Acral Ischemia, or Venous Thromboembolism?

If so, then active inhibition of thrombin by heparin therapy is probably indicated.20 It should be noted, however, that although ischemia secondary to DIC has been proposed as a major cause of organ dysfunction, including acute respiratory distress syndrome (ARDS) and acute renal failure, there is very little convincing evidence that fibrin deposition per se is a major and direct cause of these problems.2,21 In fact, ARDS frequently occurs in the absence of DIC,21 and renal failure associated with DIC is usually due to other causes than renal cortical necrosis.8,21 Therefore, it is not surprising that there is no evidence that heparin therapy has had any significant effect in these situations.

The only other instances other than those noted above where heparin therapy is probably indicated are a retained dead fetus with hypofibrinogenemia prior to induction of labor,22,24 excessive bleeding associated with a giant hemangioma,14 and neoplastic disease,25 particularly promyelocytic leukemia.26-28 The latter disorder presents special problems because of the associated compromise in thrombopoiesis secondary to both the underlying leukemia and the chemotherapy. Therefore, in these patients it is important to give enough platelet transfusions to keep the platelet count >50,000/µl and enough cryoprecipitate to keep the fibrinogen level >150 mg/dl.26,27 Since significant platelet and fibrinogen increments are not readily attainable in these patients without giving continuous infusion heparin, transfusion therapy in these patients should be given under the cover of heparin infusion. However, because of the associated thrombocytopenia, the amount of initial heparin utilized probably should be reduced to 5–10 U/kg/hr or that amount that will be sufficient to allow significant platelet and fibrinogen increments to occur following transfusion. Daily adjustments in heparin dosage and transfusion requirements may be necessary depending on clinical and laboratory parameters until the leukemia has been eradicated from the marrow (usually 5–10 days). It should be noted, however, that although in most recent series patients treated with heparin during induction have a higher rate of remission, there is no statistical significance between the heparin and nonheparin groups when the data are evaluated cumulatively.27,28

Another neoplastic disorder associated with DIC where heparin may be indicated is the patient with DIC secondary to solid tumor—usually a mucous producing adenocarcinoma.25 Because DIC is chronic in these patients (although occasionally varying in severity), it is easier to determine the efficacy of heparin therapy in patients with excessive bleeding or thrombosis by correlating careful clinical observations and serial laboratory analysis with heparin therapy. However, these patients with few exceptions usually have a very poor prognosis related to their underlying disease, and therefore heparin is, at best, only of temporary benefit.25

In contrast to the situations noted above where heparin may be indicated, in most other cases of DIC (which probably include 95% or more of patients) heparin therapy has not proven to be helpful and occasionally may be harmful.1,8,29,32 Acute forms of DIC are either brief and end with prompt treatment of the underlying disorder or the patient dies of his underlying disease. In this situation it is extremely difficult to evaluate the efficacy of heparin when the underlying disease is being aggressively treated with specific therapy. Therefore, it is not surprising that in acute forms of DIC, particularly those associated with infections, the addition of heparin therapy remains controversial.17 However, the majority of studies suggest that heparin does not diminish morbidity or mortality.1,8,29,32

One special situation that deserves comment is DIC associated with fatty liver of pregnancy. Although DIC complicating severe liver failure is an extremely complex topic that is beyond the scope of this review, in patients with fatty liver of pregnancy DIC is frequently prolonged and contributes significantly to morbidity.33 The reasons for this are probably twofold: (1) prolonged activation of blood coagulation and (2) very low to undetectable antithrombin III levels.33 The question in these patients is whether replacement of antithrombin III with concentrate or plasma would shorten the period of DIC and consequently decrease the morbidity and mortality. A recent report of a single patient with fatty liver of pregnancy treated with an antithrombin III concentrate suggests that it may be helpful.34

The mortality rate reported in series of patients with DIC due to various etiologies is 50%–85%,21 and this variation probably reflects the mortality rate of the underlying disorders and not the mortality from DIC per se. This hypothesis is supported by the fact that the mortality of DIC associated with placental abruptions is <1%,15 whereas that associated with infection and shock is 50%–80%.21 Therefore, there is no doubt that the major determinant of survival is the underlying disease and that DIC per se probably contributes little to overall mortality. For this reason, in addition to the
tremendous variations that this complication causes in individual patients, it is extremely difficult to evaluate the effects of therapy. However, it is clear that very careful clinical and laboratory observations in groups of patients with similar underlying disorders are extremely helpful in elucidating the natural history of the process, in determining its effect on the patient, and clarifying whether certain therapeutic interventions may be helpful. Therefore, the continued accumulation of careful clinical studies may be helpful in determining the proper management of DIC in homogeneous groups of patients and in given individual situations.

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