Therapeutic interventions in endotoxin-induced disseminated intravascular coagulation

Sir,

Disseminated intravascular coagulation (DIC) is a syndrome that results from of a complex interaction of coagulation and fibrinolysis. DIC is characterized by the activation of the coagulation pathway from concurrent tissue-factor dependant activation of coagulation with depression of natural anticoagulant pathways and shutdown of endogenous fibrinolysis. This leads to thrombus formation throughout the microvasculature. Consumptive coagulopathy may ensue if the fibrinolysis cascade is subsequently activated and profuse bleeding can occur, resulting from the lack of platelets and coagulation factors which were consumed in the original pervasive thromboses. Thus, DIC can cause the clinical scenario of multiorgan failure either secondary to tissue hypoxia and microinfarcts due to multiple microthrombi or consumptive coagulopathy.[1]

DIC is not a primary disease, but rather it is an acquired syndrome secondary to an underlying disorder. Common clinical conditions associated with DIC include sepsis and severe infections, trauma, malignancy, organ destruction, obstetric complications, hepatic failure, vascular disorders, and toxic or immunologic reactions.[2,3] The marked heterogeneity of the underlying disorders causes difficulty in treating DIC.[4] The proper management of patients with DIC remains controversial. However, it is widely accepted that the foundation of treating DIC has been to remove the underlying disorder or causative agent.[3] The options currently used for managing DIC include plasma and platelet transfusion, anticoagulant administration, and coagulation inhibitor administration.[5]

There have not been many clinical trials on DIC, stemming from the complexity, variability, and unpredictability of the syndrome.[1] Thus, the treatment of DIC is not based on firm evidence from double-blinded, randomized controlled clinical trials but rather is guided by clinical judgment. There have been experimental animal trials, especially in endotoxin-induced DIC. These limited experimental studies, along with systematic reviews, have provided information and guidelines for improved treatment strategies.

Plasma and platelet transfusion has been used to treat DIC cautiously to avoid further stimulation of the coagulation system. Further, concurrent heparin infusion can be given as a precaution to prevent this adverse outcome.[4] However, the efficacy of plasma and platelet transfusion also has not been proved in clinical or experimental studies[1] Transfusion should not be initiated solely on the basis of laboratory results. Rather transfusion is indicated in patients with active bleeding, in patients requiring invasive procedures, and in patients at risk for bleeding complications[5] Transfusions should be performed quickly and in large volumes. Contraindications for transfusion include patients without active bleeding, patients not requiring invasive procedures, or patients not at high risk for bleeding complications, and patients with chronic pancreatitis or hepatic damage.[6] Additionally, fresh frozen plasma is preferred to cyroprecipitate since it contains all coagulation factors and inhibitors and lacks activated factors, which could be a potential source of contamination.[2]

Heparin has been used since 1959 to treat DIC.[4] Although heparin has been shown to inhibit activation of the coagulation cascade in rabbits with DIC resulting from sepsis, it has not been demonstrated in clinical trials. Moreover, it is not considered to be safe in patients who are predisposed to bleeding or at risk for bleeding. Most reviews assert that there is no indication for the use of heparin as routine treatment for DIC.[1] However, as prophylaxis against venous thromboembolism, heparin should be given at a low-dose of 5–10 U/kg, either subcutaneously or intravenously. The only indication for high-dose heparin administration is for patients with acute DIC and thromboembolism or fibrin deposition manifested as purpura fulminans or acral ischemia.[5] Cases of chronic DIC should not be treated with heparin unless recurrent emboli are likely. Such cases include patients with solid tumors, hemangiomas, or dead fetus syndrome.[4] Low-molecular weight heparin (LMWH) has been suggested to have the same anticoagulant properties as heparin but significantly lower risk of bleeding. LMWH has been reported as effective treatment for DIC in rabbits.

Recombinant hirudin is a potent and specific inhibitor of thrombin. Although no clinical trials have begun using hirudin, it has been shown to be effective for treating DIC in animal studies.[4] Another recent agent, rNAPc2, has been

developed as a potent and specific inhibitor of the tissue factor-factor VIIa complex. It is currently being investigated in clinical trials and hopes to bring promising results.[5]

Antithrombin III (AT III) is a vital physiological inhibitor of coagulation. Low AT III levels are associated with increased mortality. AT III also has the anti-inflammatory property of reducing C-reactive peptide and IL-6 levels. It has been the most studied DIC treatment, especially in animal studies. A study in baboons has showed that AT III reduced mortality from sepsis. Administration of AT III at physiologic levels has led to improvement in organ function and shortened duration in DIC patients. Trials have shown that administration of AT III at levels above physiologic levels has reduced sepsis-induced mortality and positively impacted survival.[4,5] However, there is not enough evidence to promote routine usage of AT III in DIC.

The possible combination of AT III with heparin has also been investigated. A study of 51 patients with DIC and shock showed that treatment of AT III with heparin shortened the duration of DIC symptoms better than treatment with AT III or heparin alone.[1] An investigation of rabbits with endotoxin-induced DIC found that infusion of AT III and LMWH exerted a beneficial effect on hemostatic markers and mortality rate and was more useful in treating DIC than AT III alone.[7] Another study of endotoxin-induced DIC neonatal pigs concluded that AT III combined with tissue plasminogen activator was more advantageous in treating the clinical manifestations of DIC than either modality alone.[8] However, there are no recommendations on combination AT III treatment for humans due to lack of clinical trials.

Protein C supplementation has been rationalized based on the finding that Protein C depression may contribute to the pathogenesis of DIC. Additionally, Protein C has anti-inflammatory and anti-apoptotic properties. Administration of Protein C in experimental animals has shown to be effective.[5] Trials from the Protein C Worldwide Evaluation in Sepsis (PROWESS) showed that administration recombinant form of Protein C has reported success in reducing mortality at 28 days from 31% to 25% in patients with severe sepsis.[3] A comparative study showed that Protein C was more efficient than heparin in the treatment of DIC and improved survival times.[4]

Tissue factor pathway inhibitor (TFPI) has been postulated to be beneficial based on the role of tissue factor in thrombin generation in DIC.[5] Experiments in baboons showed that TFPI is a potent inhibitor of sepsis-induced mortality. Clinical trials have demonstrated that recombinant TFPI inhibits coagulation during endotoxemia. A phase II randomized clinical trial in patients with severe sepsis has shown a trend toward reduced 28-day mortality and an improvement in organ dysfunction.[4]

The foremost and most efficacious management of a patient with DIC is to remove the underlying cause and manage any underlying disease. In patients who have active bleeding require invasive procedures, or are at risk for bleeding complications, plasma and platelet transfusion is indicated. There is currently no evidence that treatment with heparin, LMWH, or AT III are recommended as routine treatment for DIC. While Protein C is currently indicated in the management of DIC, additional evidence is needed to strengthen the evidence.

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