Coagulation inhibitor replacement during sepsis: Useless?

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Objective: Because coagulatory activation in sepsis is triggered mainly by tissue factor release from endothelial cells and blood monocytes during their activation via proinflammatory cytokines, inhibition of coagulation by exogenous administration of coagulatory inhibitors has been proposed. These strategies should allow us to prevent and treat excessive coagulatory activation, thereby potentially preventing sepsis-induced organ dysfunction. Potential therapies include the natural coagulation inhibitors antithrombin, activated protein C, and tissue factor pathway inhibitor, as well as direct thrombin inhibition by recombinant hirudin.

Data Sources: A limited review of the published literature using all sources was undertaken.

Study Selection: Selected clinical and experimental studies with coagulatory inhibitors were analyzed.

Conclusions: The biological properties of coagulatory activation during sepsis (coagulation as a protective mechanism to control the septic focus, e.g., fibrin deposition during peritonitis) are not completely understood. Therefore, one has to be careful when administering coagulatory inhibitors, especially because patients with multiple organ dysfunction syndrome often do not show the widespread fibrin deposition in nutritive blood vessels that have been seen experimentally. How might these patients benefit from thrombin inhibition? Coagulatory activation per se seems unlikely to directly cause deterioration of organ function, although it is involved in generalized endothelial activation with consecutive mediator release and increased leukocyte-endothelial cell interaction. Antagonism of inflammatory mediators and, consecutively, endothelial cell activation might be a better target in adjunctive sepsis therapy, with improvement in septic microcirculatory disturbances. Administration of natural pleiotropic coagulation inhibitors that are documented positive effects on the microcirculation, (such as activated protein C, antithrombin) seems to be promising. (Crit Care Med 2000; 28[Suppl.]:S74–S76)

Key Words: coagulation; sepsis; microcirculation

Septic multiple organ dysfunction syndrome (MODS) is the leading cause of death in patients in the surgical intensive care unit. MODS is caused by a systemic inflammatory response of the organism to an infection and/or surgical trauma (1–6). The subsequent excessive release of proinflammatory mediators and the bacterial toxins themselves activate the coagulatory system and induce disseminated intravascular coagulation (DIC) (5, 7, 8). DIC often manifests before organ function deteriorates (9) and is associated per se with higher mortality in intensive care unit patients (5, 10–12). Therefore, DIC is considered an important pathogenic factor in the development of MODS (5, 10, 11, 13, 14). This assumption led to the hypothesis that effective treatment of coagulatory disorders and DIC would improve variables of MODS.

To evaluate this hypothesis, we present some studies, first on the relationship between coagulation and sepsis and then on the pathophysiologic link between coagulation and organ dysfunction. We will then explain our view on the role of coagulation in the pathogenesis of MODS and discuss potential side effects of coagulation inhibitors and their distinct anti-inflammatory profiles and possibilities.

Relation between Coagulation and Sepsis. The exact relation between activation of the coagulation system and inflammation has not been completely elucidated thus far. However, there are elegant experimental studies that clarify this connection. In human whole blood cell culture systems, coagulatory activation by tissue factor is potentiated by endotoxin, leading to a massive release of proinflammatory cytokines such as interleukin (IL)-8 (15). Effective inhibition of inflammatory mediators in experimental sepsis by the respective monoclonal antibodies resulted in an effective modulation of the inflammatory coagulatory disturbances (16, 17), whereas administration of proinflammatory cytokines or endotoxin in human volunteers induced coagulatory alterations similar to those observed in septic coagulatory activation (8, 18, 19). The intrinsic pathway of coagulation has been shown to contribute to hemodynamic disturbances, which are comparable to changes observed in septic shock (9, 20).

Relation between Coagulation and Organ Dysfunction. Sepsis-induced formation of fibrin thrombi in the capillary system of vital organs is generally thought to be responsible for decreased organ perfusion and subsequent organ failure (9, 11). This seems to contradict the observation that patients with MODS only infrequently show the widespread fibrin deposition in nutritive blood vessels that has been seen experimentally (21). The reason for this observation is not completely clear thus far. It is possible that capillary fibrin deposition is simply an epiphenomenon of shock and produced by malperfusion. But if fibrin deposition per se is not responsible for organ dysfunction, how would patients with sepsis benefit from isolated coagulatory inhibition?

Revised Concept of the Role of Coagulation in Septic Organ Dysfunction. We favor another hypothesis on the role of...
Therefore, increased leukocyte-endothelial cell interaction and not coagulatory activation per se might be the key mechanism in the development of organ dysfunction (34). This view is supported by clinical and experimental studies. First, a clinical study showed that neutropenic patients are unlikely to develop septic acute respiratory distress syndrome (35). Second, experimental inhibition of coagulation (eg, by antithrombin) improved mortality without significant improvements in coagulation (36), and third, the anticoagulant heparin improved coagulopathy without reducing mortality (37).

It therefore seems possible that inhibition of coagulatory activation may only indirectly modulate the development of organ dysfunction, eg, by the modulation of endothelial cell activation, which should therefore be a primary target (in addition to the leukocyte itself) of pharmacologic interventions.

Use of Coagulatory Inhibitors in Sepsis: Potential Side Effects. From a practical point of view, we have to consider several potential side effects of coagulatory inhibitors in septic patients. In some patients, anaphylactoid reactions may occur. Bleeding disorders have been reported with the use of antithrombin in combination with heparin and with combined tissue factor pathway inhibitor and hirudin treatment (38, 39). If plasma products are used (antithrombin), there is a risk, although minimal, of infection with the virus or hepatitis human immunodeficiency virus, depending on the production and purification procedure.

Use of Coagulatory Inhibitors during Sepsis: Limitations. Another crucial point is the appropriate and critical selection of patients; should all septic shock, trauma, and critically ill patients be treated? This is a highly important question because not all these patient groups benefit from coagulation inhibitor supplementation to the same degree (40). The time point of the intervention and the duration of coagulatory inhibitor substitution seem to be crucial factors in effective therapy (39, 41). It remains unclear thus far at what point coagulatory inhibitors should be started, at what dosage they should be given, and for how long therapy should be continued. Should therapy be given for as long as the coagulatory inhibitor is consumed, as long as sepsis persists, or as long as shock persists?

Use of Coagulatory Inhibitors in Sepsis: Antithrombin. High-dose antithrombin supplementation showed additional effects on microcirculation during experimental endotoxemia, whereas low-dose antithrombin only modulated coagulation (42). In a controlled clinical trial, only long-term (14 days) and high-dose antithrombin supplementation (activity >120%) modulated inflammatory mediators and coagulatory variables, mainly during the second week of application (43). Therefore, it remains questionable whether the 4-day period of application that is currently used in most clinical sepsis trials is enough time for the coagulation inhibitor to work effectively. Finally, the costs of additional treatment with coagulatory inhibitors must be evaluated, especially if expensive drugs are used.

Use of Coagulatory Inhibitors in Sepsis: Singular Factor Inhibition or Pleiotropic Intervention. In general, inhibition of singular coagulation factors (eg, thrombin inhibition by hirudin) seems not to be promising in treating coagulatory disorders in sepsis (44). When a very specific substance modulating at the beginning of the coagulation cascade is used, proximal mediators are produced without limitations. This uncontrolled proximal mediator explosion could perhaps lead to even more endothelial cell activation and endothelial cell damage. At the same time, the positive effects of coagulatory proteins may also be prevented (eg, thrombin-induced increase in fibrinolysis) under such conditions.

The administration of natural pleiotropic coagulation inhibitors (eg, activated protein C and antithrombin) seems to be a promising approach because these substances have been shown to have multiple mechanisms of action (39, 41). The combination of anticoagulatory and anti-inflammatory substances should be tested under clinical conditions. In our efforts to develop new anti-inflammatory and new coagulatory strategies, we should keep in mind that the benefit of all adjunctive therapies in sepsis will depend on the effective treatment of the septic focus with conventional therapy.


