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Antithrombosis Trials: Should we test therapeutic heparin adjusted based on activated partial thromboplastin time in septic shock?*

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Retrospective analysis of several studies suggested that heparin treatment might be beneficial in septic patients (1–4). In this issue of *Critical Care Medicine*, Jaimes et al (5) present the results of the first large, prospective randomized controlled trial of intravenous heparin for sepsis. Given at a fixed dose of 500 U/hr for up to 7 days, heparin vs. placebo had no significant beneficial effect on all-cause mortality (19 of 159 [12%] vs. 22 of 160 [14%]), respectively, $p = 0.63$; daily reduction in multiorgan dysfunction score (mean $\pm$ 95% confidence interval) ($-0.13 \pm [-0.16 \text{ to } -0.11]$ vs. $-0.11 \pm [-0.14 \text{ to } -0.08]$, respectively); or median [interquartile range] hospital length of stay (13 days [8 to 20] vs. 12 days [6–18]). Importantly, bleeding risk was assessed daily by monitoring the activated partial thromboplastin time (aPTT). Possibly, as a result, there was no significant increase in bleeding associated with heparin, because any patient in the trial with an aPTT greater than 60 seconds (42 of 319 patients) had treatment terminated.

The authors should be commended for undertaking this large sepsis trial of heparin therapy and their efforts to maintain double blinding. However, there are several aspects of the trial that limit its interpretation. The population studied had a relatively low-control mortality rate (14%), and therefore, the results may not be applicable to more severely ill septic patients. In studies of other antithrombotic agents in sepsis, when benefit was found in subgroups, it was among patients with a higher risk of death (1, 6). Also, the dose of heparin used by Jaimes et al was lower than standard therapeutic dose heparin (7). Furthermore, despite this relatively low dose, a quarter of the patients treated with heparin (38 of 159) were still eliminated from the study (although included in the intention-to-treat analysis) before completing the 7 days trial because of an elevated aPTT. Thus, treatment may have been inadequate to achieve a beneficial effect in many patients. In contrast to this study, a recent retrospective analysis of higher risk septic patients reported that therapeutic dose heparin administered for concurrent problems and presumably adjusted (but not terminated) based on aPTT levels was associated with improved survival (8).

Despite these potential limitations, Jaimes' prospective results add to those of three other antithrombotic agents questioning the pathogenic role of thrombosis in sepsis and the

*See also p. 1185.

effectiveness of this therapeutic approach (1, 2, 4, 6, 9–17). Previously, recombinant human activated protein C (rhAPC), tissue factor pathway inhibitor, and antithrombin III were tested in Phase II and III trials. All showed no significant benefit except one testing rhAPC (1). However, subsequent controlled trials of rhAPC in different septic populations (adults with a low risk of death and pediatric patients) did not show benefit (9, 16). In part, because of these inconsistent effects, additional trials (PROWESS–Shock, RESPOND, and APROCCHS trials) (18–20) testing rhAPC in high-risk adult septic patients are now underway and enrolling patients. These trials will hopefully help us understand why rhAPC seemed beneficial in the first but not subsequent Phase III trials.

Assuming, however, that thrombosis does indeed have an important role in the pathogenesis of sepsis, there are several reasons why heparin represents an antithrombotic agent that deserves further study. Although heparin was not beneficial in the study by Jaimes et al, it also did not increase the risk of bleeding. In contrast to heparin, protocols to monitor bleeding risk and to adjust dosing accordingly are not readily available for the other three antithrombotic agents tested in sepsis, and each has been associated with increased bleeding in large trials (1, 2, 4, 9, 16). Other reasons supporting an additional clinical trial of heparin in sepsis include the following: 1) it is relatively inexpensive; 2) it has been used extensively and successfully in other critical illnesses, such as deep venous thrombosis, pulmonary embolism, and acute coronary syndrome; 3) it has been shown to be highly effective at preventing thrombosis formation and accelerating its resolution; and 4) methods to adjust its dose on a weight basis have been well worked out to maximize benefit and minimize risk. Although similar dose adjustments might be possible for other antithrombotic agents, defining the appropriate measures and developing effective protocols to monitor and reduce their hemorrhagic risk would require substantial investigation.

On the basis of these reasons, we believe an additional large randomized controlled trial of heparin in sepsis is warranted. However, such a trial, in contrast to this one by Jaimes et al, should include a patient population with a higher risk of death and therapy should be adjusted based on therapeutic aPTT values as is conventionally done in other critical illnesses. Without such adjustment, under-treatment in some patients and overtreatment in others might negate any potential benefit of heparin for sepsis. In the absence of such a study, it is difficult to conclude that heparin has been fully tested and has no role in the treatment of sepsis. Importantly, patients with sepsis are a vulnerable group, and even with heparin therapy adjusted based on aPTT, the safety of such a study would have to be closely monitored.

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