Commentary

Antithrombin and hypercoagulability in sepsis: insights from thrombelastography?

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See related research by Gonano *et al*., http://ccforum.com/content/10/6/R160

Abstract

Antithrombin (AT) has been used for over 25 years to successfully treat disseminated intravascular coagulation (DIC). A four-day AT therapy in patients with DIC in the KyberSept trial has been related to a clear survival benefit in patients not receiving concomitant heparin. Gonano and coworkers performed thrombelastography (TEG) measurements in patients with severe sepsis and clearly showed hypercoagulability, as defined by five TEG parameters, compared to healthy controls. In the AT group they found a trend towards normalization of TEG parameters after treatment, although this did not reach statistical significance. This first clinical evaluation of hypercoagulability during AT treatment could not provide evidence for an attenuation of coagulopathy, an effect that might be due to high inter-individual variability.

In a recent paper, Gonano and coworkers [1] reported the potential failure of antithrombin (AT) therapy to modulate hypercoagulability, as evident from TEG measurements. AT constitutes the principal physiological inhibitor of thrombin and of other serine proteases of the clotting cascade, and has been shown to interfere with the clotting process at various sites [2]. AT activity is decreased in patients with trauma, shock and sepsis by virtue of its consumption during complex formation with clotting factors, and by degradation via granulocyte elastase [3]. The first application of AT in a patient with septic shock complicated by disseminated intravascular coagulation (DIC) was described in 1978 [4]. Following this report, many intensive care specialists have also used this natural coagulation inhibitor over more than 25 years to treat coagulopathy in patients with sepsis complicated by DIC. The KyberSept trial investigated the effects of a four-day AT therapy in 2,314 patients with severe sepsis [5]. In this study, AT treated patients did not benefit overall in terms of 28-day and 90-day mortality. In a recent subgroup analysis, however, concomitant heparin application was characterized as the major reason for the failure of the AT treatment; 28-day as well as 90-day mortality were improved in patients not receiving concomitant heparin during the treatment phase [6]. Given that AT was clearly more effective in KyberSept patients with DIC than those without it [7], the characterization of AT's actions on hypercoagulability in sepsis clearly seems to be interesting and important.

In a recent issue of *Critical Care*, Gonano and co-workers [1] analyzed hypercoagulability in a subset of patients in the KyberSept trial by thrombelastography (TEG) and routine coagulation tests. They presented data from 16 placebo and 17 AT treated patients receiving concomitant heparin. Septic patients in both groups clearly showed hypercoagulability, as defined by five TEG parameters, when compared to normal values. This information may be important given that the severity of coagulatory disorders has been clearly correlated with decreased survival, and because the International Society of Thrombosis and Hemostasis score is a perfect predictor of mortality [8]. Characterization of septic coagulopathy by TEG has not been published thus far, and the clinical relevance of these measurements has to be determined in further studies.

Coagulatory parameters during high dose AT supplementation have already been extensively characterized in four-day studies [9] as well as during long-term (14-day) treatment [10]. All studies clearly show a reduction in the severity of DIC with the administration of AT when measured with standard coagulation tests [9-11]. Thus far, no studies looking at TEG measurements in this scenario have been performed.

At least for us, it remains unclear from the given data whether AT therapy really is unable to influence hypercoagulability, as

AT = antithrombin; DIC = disseminated intravascular coagulation; TEG = thrombelastography.

was indicated in the study by Gonano and colleagues [1] by TEG measurements with high inter-individual variability. Despite this variability, in this pilot trial with 33 patients, the group treated with AT also showed an attenuation of hypercoagulability after an intravenous bolus of AT, and no differences in the later time course when compared to controls without AT. It could be speculated that this AT effect will gain statistical significance in a better powered trial. One problem with the KyberSept trial design in terms of efficacy in hypercoagulability could be the treatment period of only four days. In other studies, however, a four day treatment period has allowed AT to become effective with regard to DIC [10].

There is some evidence from a small clinical pilot trial that prolonged AT supplementation with adjusted activity (>120% activity) can modify coagulatory parameters [10]. However, the validity of this concept of prolonged, dose-adapted AT support has not been further established by the literature. From the given data it seems to be debatable whether AT action in septic patients is really dependent on its effect on hypercoagulability. Other key mechanisms could include the microhemodynamic and cellular actions of AT during endotoxemia [11]; AT was shown to effectively prevent endotoxin-induced leukocyte adhesion to the endothelium and to improve capillary performance, both of which are known to be crucial during the development of multiple organ dysfunction in sepsis.

Since TEG has been shown to be a highly sensitive assay for hypercoagulability, TEG measurements may indicate distinct changes in coagulation in septic patients that can not be measured by standard tests. After correlation of these laboratory findings with clinical data, TEG may become important for future trials investigating pharmacological anticoagulation strategies in patients with severe sepsis.

Competing interests

JNH has received honoraria for oral presentations from Biotest, CSL-Behring, Fresenius and Octapharma. JNH has a scientific cooperation sponsored by CSL-Behring.

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