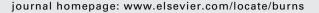


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Review

Replacement of specific coagulation factors in patients with burn: A review

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ABSTRACT

Major burn is often associated with inflammation and coagulation system activation, consumption of endogenous coagulation factors, which have been associated with adverse clinical outcome. Coagulation system dysfunction during early postburn period is characterized by activation of procoagulation pathways, enhanced fibrinolytic activity and impairment of natural anticoagulants activity. Treatment principles focused on the normalization of coagulation and the inhibition of systemic inflammation might have a positive impact on organ function and on the outcome in septic burn patients. Modern treatment strategies using antithrombin, protein C and recombinant factor VIIa are based on early and continuous assessment of the bleeding and coagulation status of burn patients. This allows specific goal directed treatment, thereby optimizing the patient's coagulation status early, minimizing the patient's exposure to blood products, reducing costs and improving the patient's outcome.

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1. Introduction

Major burn is often associated with inflammation and coagulation system activation, consumption of endogenous coagulation factors, which have been associated with adverse clinical outcome [1,2].

The management of burn patients has improved with a better understanding of burn-induced coaguplopathy. Coagulation abnormaliteis in burn patients were assumed to include three main components: primary coagulopathy at early phase of burn due to the introduction of cellular debris from burned tissues into the circulation, coagulopathy following septic complications and coagulopathy associated with surgical procedures.

Coagulation system dysfunction during early postburn period is characterized by activation of procoagulation pathways, enhanced fibrinolytic activity and impairment of natural anticoagulants activity. Both thrombotic and fibrinolytic pathways are triggered proportionally to the extent of the burn [2-5]. Early activation of coagulation can be considered instrumental in containing inflammatory activity to the site of injury. Microthrombi formation within the immediate vicinity of burn is essential for maintaining the integrity of microcirculature surrounding the burn wound. However, the generalized systemic microthrombi formation may lead to reduction in organ perfusion. The relationship between coagulation and inflammation may have major consequences for the pathogenesis of microvascular injury and subsequent multiple organ dysfunction or failure [6]. The coagulation system abnormalities are most pronounced during the first week after injury and may be further enhanced by surgery. Excision of burn wounds may be associated with extensive blood loss, dilution and consumption of coagulation factors which may have an additional negative impact on the coagulation system.

Burn patients are also at a high risk for development of septic complications. The activation of inflammatory and coagulation cascade in septic burn patients can ultimately lead to multi-system organ failure and increased mortality. Even with advances in critical care techniques, the mortality rate from severe sepsis in burn patients varies from 28% to 65% and is higher than the mortality rate of other trauma and general critical care populations [7]. Treatment principles focused on the normalization of coagulation and the inhibition of systemic inflammation might have a positive impact on organ function and on the outcome in septic burn patients.

Several coagulation factors are available and can be substituted selectively in patients with severe burn.

As the volume and quality of evidence in this field accumulates, clinical practice guidelines providing evidence-based recommendations should be developed by a multidisciplinary task force with respect to the management of the burn patient with bleeding and coagulopathy, which, when implemented, may improve patient outcomes. Until then, more specific focus on the use of specific coagulation factors in burn patients may be helpful. In this article the effort has been attempted to review the evidence for and against the use of these novel potential therapeutic tools to manage coagulation abnormalities in burn patients.

2. Clinical applications of natural anticoagulant factor concentrates in burn patients

Molecular pathways contributing to inflammation-induced activation of coagulation and modulation of inflammation by coagulation factors have been reported in the literature over the last decade. Endothelial bound anticoagulant mechanisms, the protein C system, the antithrombin (AT) system and the tissue factor pathway inhibitor (TFPI) system play important roles in this respect [2]. The coagulopathy seen in burn patients is associated with the marked depletion of the endogenous regulators of the coagulation system. An early decrease in coagulation inhibitors levels in burn patients is associated with poor clinical outcome [5,8,9].

In view of the central role of physiological anticoagulants at the interface between coagulation and inflammation, therapies aimed at improving the inhibition of coagulation and thereby modulating inflammatory activity have been developed and evaluated in clinical trials. Several coagulation factors are available and can be substituted selectively; in this section, a brief overview of those most commonly used is given.

2.1. Antithrombin

Antithrombin replacement therapy has been used in burn patients since the 1980s. Plasma levels of antithrombin are low in burn patients and are an independent predictor of clinical outcome [2,9]. Antithrombin concentrate infusion in burn patients has been evaluated in a number of small clinical trials. All trials demonstrate some beneficial effect on disseminated intravascular coagulation (DIC), or improvement of organ function. However, all trials use highly variable criteria for assessing DIC and organ dysfunction and for this reason comparison of trial results seems to be difficult.

Niedermayr et al. [9] evaluate the incidences of AT deficiency in severe burn and its correlation to the variables of the abbreviated burn severity index (ABSI), length of hospital stay (LOS) and mortality in 201 patients suffering from severe burn. One hundred and eight patients (54%) developed AT deficiency during their hospitalization and received substitution therapy by continuous infusion to maintain physiological plasma activity (70-120%). The percentage of patients in an AT deficient state was highest within the first 5 days after injury. It was 26% on day 1 and between 38% and 41% on days 2-5 and it thereafter decreased constantly over time. Several factors may explain these findings: dilution due to initial fluid resuscitation, loss toward the interstitial compartment and increased consumption caused by the development of burn associated systemic inflammatory response syndrome (SIRS). Reasons for the late onset of AT deficiency can be explained by burn wound infections and other hospital acquired infections with and without development of concomitant liver dysfunction, sepsis or septic shock. Total body surface area burned (TBSA) and inhalation injury show significant influence on the development of AT deficiency (p-values 0.0001 and 0.037). TBSA and a presence of inhalation injury had a significant impact on the amount of AT concentrate necessary to maintain normal

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