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FOCUS EDITORIAL

ICM focus on thrombosis and bleeding

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Prevention of venous thromboembolism in the ICU

Intensive care unit patients are high risk of developing thrombotic complications such as deep venous thrombosis (DVT) and pulmonary embolism (PE) [1]. Indeed, due to the hypercoagulative state typical for many forms of critical illness [2–4] associated with risk factors as prolonged immobilisation or the use of intravascular devices, ICU patients are at higher risk for thrombotic complications.

Prevention of venous thromboembolic events is typically performed with prophylactic pharmacologic treatment, chiefly low molecular weight heparin (LMWH) in Europe [4, 5]. A recent meta-analysis including 5500 patients reported that LMWH may be more effective than unfractionated heparin (UH) for DVT prevention, but remains inconclusive regarding prevention of pulmonary embolism, risk of bleeding or mortality [6]. The most commonly used route used is by subcutaneous injection, which may not be optimal in the critically ill due to the use of vasopressors related vasoconstriction and fluid resuscitation related tissue oedema [7, 8].

Bleeding in the intensive care unit

Critically ill patients in the intensive care unit (ICU) are at risk of developing bleeding. In an international 7-day inception cohort study (11 countries, 97 ICUs, 1043 patients), the prevalence of clinically important gastrointestinal (GI) bleeding was 2.6% among acutely admitted adult ICU patients, and 4.7% had at least one episode of overt GI bleeding during the ICU stay [9]. Median time from ICU admission to bleeding was 3 days. Importantly, three out of four patients received acid suppressants at least 1 day during the ICU stay, which may have prevented some—but not all—types of GI bleeding [10]. In the recently published Surviving Sepsis Campaign 2016 guideline, a strong recommendation (low quality evidence) in favor of using acid suppressants in high-risk ICU patients was issued [11]. A subset of high-risk patients seems to be patients on extracorporeal life support (ECLS). Among 132 patients treated with ECLS in Baltimore, MD, USA, 18 patients (13.6%) experienced overt GI bleeding [12]. A French single-centre observational study ($n = 135$) combined with a systematic review assessed the risk of brain injury, including bleeding, during venovenous ECLS [13]. The reported frequency of cerebral bleeding was 5–7%, it occurred early during ECLS, and was associated with a high mortality rate. The high prevalence of bleeding in patients on ECLS may in part be a result of multifactorial coagulopathy, including thrombocytopenia and anticoagulation with heparin. An updated systematic review and meta-analysis of randomized clinical trials (RCTs) compared anticoagulation with heparin vs citrate for continuous renal replacement therapy (CRRT), and found a 64% lower risk of bleeding in patients receiving citrate for CRRT, as compared to systemic heparin [14]. The same magnitude of effect was found when comparing citrate to regional heparin, although not statistically significant.

An Italian single-centre RCT ($n = 38$) assessed use of protein C zymogen vs. placebo in high-risk ICU patients with severe sepsis/septic shock [15]. The study was stopped early because of safety issues: the composite primary outcome of prolonged ICU stay and 30-day mortality was 79 vs. 67%, in-ICU mortality was 79 vs. 39%, and 30-day mortality was 68 vs 39% in the protein C zymogen group vs the placebo group. Concordantly, a systematic review with meta-analysis and trial sequential analysis assessed use of antithrombin III (AT III) in critically ill patients (30 RCTs, 3933 patients), and found no benefit of AT III in critically ill patients in general or in different subgroups of critically ill patients [16]. Importantly, use of AT III significantly increased bleeding events.

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Hemorrhagic shock is a life-threatening condition and prompts early and immediate identification and treatment [17]. One of the cornerstones is fluid and blood product resuscitation, i.e. damage control resuscitation. An international prospective cohort study of severely injured bleeding trauma patients (three major trauma centers, 106 patients) showed that damage control resuscitation with standard doses of blood components was inadequate at correcting trauma-induced coagulopathy during hemorrhage, and optimization of damage control resuscitation strategies may be warranted [18].

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