Editorial

Heparin thromboprophylaxis in critically ill patients: Is it really changing outcome?

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One and half century ago, Father of modern pathology, Rudolf Virchow, described the pathogenesis of thrombosis, known as Virchow's Triad, which comprises stasis, hypercoagulability of blood and vessel wall damage. The components of the triad is present in the majority of critically ill patients, making them vulnerable to developing deep venous thrombosis (DVT) and subsequently pulmonary embolism (PE), collectively known as venous thrombo embolism (VTE); which is among preventable causes of hospital-acquired morbidity and mortality in ICU patients. The incidence of DVT in the intensive care unit (ICU) ranges from 15-60% (high in patients with ischemic stroke and trauma).[1] In the majority, these thrombi occur within first week of hospitalization in the ICU and start to form in the valve cusps of calf deep veins. Signs and symptoms of DVT are usually masked in critical illness and DVT remains clinically silent in up to 95% cases.[2]

Due to the presence of risk factors, including but not limited to immobilization, sepsis, surgery, trauma, organ failure (heart or respiratory), malignancy, pharmacological sedation and paralysis, indwelling catheter in major vessels, vasopressor etc., thromboprophylaxis has become an integral part of prescriptions for critically ill patients. Thus, for the last two decades despite unavailability of evidence about any direct association with decreasing rate of ventilator-associated pneumonia, deep venous thromboprophylaxis remains an important intervention related to ventilator care called 'Ventilator Bundle' to improve patient outcome. In this issue of the Indian Journal of Critical Care Medicine, Saigal *et al.* critically evaluated recent studies on thromboprophylaxis in medically and critically ill patients.[3]

Since the first randomized control trial (RCT) by Cade from Australia in 1982, which demonstrated efficacy of thromboprophylaxis by heparin use in ICU patients, many other trials found the same.[4] Recently Alhazzani *et al.*, did systematic review and meta-analysis of seven RCTs of heparin (unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH)) thromboprophylaxis in medical-surgical critically ill patients, with exclusion criteria of pediatric, trauma, neurosurgery or cardiac surgery population.[5] In this meta-analysis, use of any heparin therapy (UFH or LMWH) was found with significant reduction (~50%) of incidence of DVT (low quality of evidence) as well as PE (moderate quality of evidence); while comparing LMWH to UFH, no difference in the incidence of DVT but lesser incidence of PE (low quality of evidence) were found. Also, no benefit on overall ICU mortality was demonstrated (moderate quality of evidence) by using any heparin thromboprophylaxis. Among the side effects, bleeding did not increase significantly with any heparin thromboprophylaxis ((low quality of evidence); while incidence of heparin-induced thrombocytopenia (HIT) reduced significantly with use of LMWH in comparison with UFH (moderate quality of evidence).

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Low-molecular-weight heparin, being more selective for inhibition of factor Xa, high bioavailability, predictable anticoagulation effect, single daily dose, and less incidence of HIT, its uses increase in ICU patients in the recent years. Serum anti-Xa level measurement could be considered to know LMWH activity as well as a surrogate marker to quantify bleeding risk (<0.40 IU/ml considered safe). In a systematic review of use of LMWH as thromboprophylaxis in critically ill patients in medical, surgical, trauma and mixed ICU settings, Ribic *et al*., analyzed 9 studies (8 prospective cohorts and one RCT).[6] Different LMWH (dalteparin, nadroparin, certoparin, enoxaparin with recommended doses) were used in these studies. Eight studies reported serially measured anti-Xa levels, mostly with the peak levels found well below 0.40 IU/ml. In this review, they found conflicting results in different studies on anti-Xa levels affected by vasopressor; while its level is not affected by the presence of edema.

A double blind RCT, evaluating different doses of enoxaparin (40 mg once-daily (OD), 30 mg BID, 40 mg BID or 1 mg/kg OD) administered for 3 days in critically ill patients revealed, at steady state, mean peak anti-Xa levels, which were 0.13, 0.15, 0.33 and 0.40 IU/ml, with respective doses; highlighted suboptimal dosing of enoxaparin with currently recommended (40 mg OD in Europe; 30 mg BID in North America).[7] In a study on safety of dalteparin (5000 IU until ICU discharge or for a maximum of 30 days) in patients with severe renal insufficiency (<30 ml/min), bioaccumulation of the drug has been ruled out, as trough anti-Xa level were less than 0.40 IU/ml in all studied patients.[8]

In the majority of studies, the clinical outcome of heparin thromboprophylaxis for DVT is very well assessed by compression or Doppler ultrasound screening surveillance of bilateral lower extremities, though 10% of all cases of DVT involve the upper extremities. On the other hand, it is difficult practically to assess true incidence of PE, which may be under reported (there are 20-45% discrepancy rate between premortem and postmortem diagnoses) due to undetected subclinical PE, among ICU patients.

Despite heparin thromboprophylaxis in critically ill patients, reported incidence of DVT was: 7.5% (114 events/1521 patients) in meta-analysis by Alhazzani; and 13.8% (45/326 patients) in systematic review by Ribic *et al*.[5,6] The incidence of non leg DVT on heparin thromboprophylaxis was found 2.2% in a recently published large prospective study (3746 ICU patients).[9]

As per Cochrane database review, Kakkos *et al*., revealed that the incidence of VTE is further reduced when pharmacological prophylaxis is combined with mechanical (intermittent pneumatic leg compression, IPC) after major orthopedic surgery.[10] Newer oral anticoagulants (dabigatran, rivaroxaban, apixaban and edoxaban) have recently been approved for prevention of VTE after major orthopedic surgery, as many studies suggest their superiority or non-inferiority to LMWH. But, these oral drugs as well as Fondaparinux (ultra low molecular weight heparin, ULMWH) have not been evaluated in critically ill patients for their efficacy and safety.

At present, available evidences suggest that all ICU patients should be considered for heparin thromboprophylaxis,[11] though this will not ensure absolute prevention from VTE and there should be constant vigilance for possibility of VTE. Probably there is a long way to go to find ideal thromboprophylxis in critically ill patients with further studies like optimal dosing or superiority of any particular heparin with safety; efficacy and safety of available newer oral anti-coagulants and ULMWH; combining with mechanical prophylaxis; extended therapy after ICU discharge.

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