Adequate thromboprophylaxis in critically ill patients

Levi, M.M.

Published in:
Critical Care

DOI:
10.1186/cc8949

Link to publication

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
In this issue of *Critical Care*, Robinson and colleagues [1] investigate the effect of increasing doses of the low molecular weight (LMW) heparin enoxaparin (commonly used as prophylaxis against venous thromboembolism [VTE]) on systemic heparin concentrations, expressed as anti-factor Xa levels. VTE is a common complication in critically ill patients. Reported rates for deep venous thrombosis in patients admitted to the ICU range from 22 to 80% depending on patient characteristics.

Thrombo prophylaxis with unfractionated or LMW heparin lowers the risk for deep venous thrombosis by more than 50% [2]. Nevertheless, the risk of VTE in critically ill patients is still much higher than in other patient groups. Amongst several factors that may explain the higher incidence of VTE in critically ill patients, such as full immobilisation or withholding anticoagulant prophylaxis because of a high bleeding risk, it was hypothesized that limited bioavailability (that is, lower plasma anti-factor Xa activity) of subcutaneously administered heparin in those patients with impaired peripheral circulation, due to vasopressor medication to maintain central blood pressure, might be important. Indeed, in a first comparative trial it was shown that critically ill patients on high dose vasopressor medication had much lower anti-factor Xa concentrations after the subcutaneous administration of LMW heparin in comparison with intensive care patients that had lower doses of vasopressor or in comparison with patients in the surgical ward [3]. A subsequent study also found consistently lower anti-factor Xa levels after subcutaneous heparin in critically ill patients [4]. In another similar study, critically ill patients with excessive subcutaneous oedema had lower anti-factor Xa concentrations compared to a control group without oedema [5]. This observation was confirmed in a group of critically ill multiple trauma patients, who showed variable and low heparin concentrations after subcutaneous injections [6].

Robinson and colleagues [1] compared plasma anti-factor Xa levels after the subcutaneous administration of the LMW heparin enoxaparin at the conventional dose (40 mg) and at increasingly higher doses (up to 70 mg) in intensive care patients. They found a dose-dependent increase in peak anti-factor Xa levels (4 hours after the injection) ranging from 0.13 IU/ml at the conventional 40 mg dose to 0.29 IU/ml at the 70 mg dose. Considering that optimal efficacy and safety of LMW heparin for thromboprophylaxis in orthopaedic and abdominal surgery was achieved with dosages of heparin resulting in peak plasma anti-factor Xa activities ranging between 0.25 and 0.30 IU/ml [7], it may be concluded that critically ill patients need much higher doses of LMW heparin than other patients. Based on the findings of Robinson and colleagues, the subcutaneous dose of LMW heparin should be increased to 60 mg daily. Alternatively, direct intravenous administration of (LMW) heparin may be considered; however, experience with this type of thromboprophylaxis is limited.

The mechanism by which critically ill patients have lower anti-factor Xa levels after subcutaneous administration of heparin is not completely understood. The
initial hypothesis was that patients on high dose vasopressor medication had impaired subcutaneous blood flow and thereby limited ability to adsorb the subcutaneous heparin [3]. An alternative explanation is that the presence of oedema hinders the absorption of heparin, although that hypothesis was not proven [5]. In addition, it has been suggested that systemic inflammation and associated multiple organ dysfunction may have an impact on heparin binding to plasma proteins and drug metabolism [8].

The clinical relevance of lower anti-factor Xa levels after conventional doses of (LMW) heparin in critically ill patients is also not totally clear. Theoretically, the low anti-factor Xa levels may lead to suboptimal prophylaxis and could indeed be a contributory factor to the higher incidence of thromboembolic complications in critically ill patients despite routine thromboprophylaxis. However, this has never been demonstrated in a clinical study. Based on the observations of Robinson and colleagues and others, a randomized controlled trial with conventional versus higher doses of thrombosis prophylaxis in critically ill patients aiming at the reduction of the incidence of VTE and other clinically relevant outcomes is justified. Such a study would also enable the evaluation of bleeding complications related to the administration of prophylactic heparin, as intensive care patients are at higher risk for hemorrhage as well [9,10].

In summary, there is ample evidence that conventional thromboprophylaxis leads to lower systemic heparin levels in critically ill patients. It is not clear whether this contributes to the relatively high incidence of VTE in intensive care patients. A clinical trial evaluating higher doses of heparin for prevention of VTE and assessing the bleeding risk of such an approach is justified.

Abbreviations
LMW = low molecular weight; VTE = venous thromboembolism.

Competing interests
The author declares that he has no competing interests.

Published: 21 April 2010

References

doi:10.1186/cc8949
Cite this article as: Levi M: Adequate thromboprophylaxis in critically ill patients. Critical Care 2010, 14:142.