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Thromboprophylaxis for Intensive Care Patients

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Authors' contributions

This work was carried out in collaboration between both authors. Author SR drafted the manuscript. Author PT revised the manuscript. Both authors read and approved the final manuscript.

Review Article

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ABSTRACT

The advent of low-molecular-weight heparin (LMWH) marked a new chapter in the prevention of venous thromboembolism. The enviable pharmacokinetic properties associated with this class of medication, ensured the place of LMWH as an attractive, if albeit more expensive alternative to unfractionated heparin. Predictable and reproducible dose response continues to negate the need for monitoring in most patient groups, while the availability of antidotes further boosts the safety profile of LMWH. These agents have long proven their worth in the medico-surgical patient population. However we have recently shown in randomised studies, that LMWH at the current recommended dose may not be as effective for critically ill patients. Critically ill patients encompass that population of patients with profound disturbance of physiology, who are at imminent risk of death and in need of continuous care. Such patients have proven to be somewhat resistant, and current evidence indicates that they may benefit from a higher dose of LMWH. A difficult undertaking, considering the heterogeneity of this population, as well as their predisposition to both haemorrhage and thromboembolism. A variety of new oral antithrombotics has recently become available for use among certain patient populations, but has not yet been studied in the intensive care unit (ICU) setting. These agents have been associated with increased risk of bleeding, and as yet, a definitive strategy in the event of major bleeding does not exist. In addition, they are more costly when compared with LMWH. All the aforementioned factors combine to make the new oral agents, unattractive alternatives for thromboprophylaxis in the ICU population.

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1. INTRODUCTION

Intensive care unit (ICU) patients are predisposed to venous thromboembolism (VTE). This can be attributed to an increasingly older clientele, trauma, sepsis, the presence of comorbidities such as: cardiac failure, renal failure, cancer, obesity, as well as the need for mechanical ventilation, sedation, decreased mobility, invasive monitoring, and surgical procedures [1-3].

The risk of VTE is approximately 1% per day among some subgroups of ICU patients [4]. A recent prospective cohort study found the rate of pulmonary embolism and deep venous thrombosis (DVT) were 18.7% and 19.9% respectively among mechanically ventilated patients in a medical ICU despite the use of chemical prophylaxis in over half of these patients [5]. VTE is often clinically silent in this patient population, and a high index of suspicion must be maintained.

The development of VTE further burdens the already limited physiological reserves of such patients. Cook et al observed longer duration of mechanical ventilation, longer periods of hospitalisation and greater mortality when intensive care patients developed VTE [6].

ICU patients are also predisposed to bleeding because of the presence of comorbidities, thrombocytopenia, platelet dysfunction, and prolonged global tests of coagulation. Many ICU patients experience minor bleeds. *Major* or *fatal* bleeding is associated with abnormal coagulation tests but not with prophylactic anticoagulants [7,8].

The most significant adverse events associated with thromboprophylaxis include bleeding, and moderate thrombocytopenia. As mentioned above, major or fatal bleeding is very rare in the ICU, whereas VTE is relatively more common. A delay in starting thromboprophylaxis was associated with an increased risk of mortality in patients on the ICU [9]. Many ICU physicians therefore feel that the risk-benefit ratio generally favours use of thromboprophylaxis [8].

2. LOW-MOLECULAR-WEIGHT HEPARIN

Low- molecular-weight heparin (LMWH) is often employed as a safe and effective means of prophylaxis [10,11] against VTE in medical and surgical patients. In the PREVENT trial, acutely ill medical patients were randomly assigned to receive either subcutaneous (sc) dalteparin 5000 IU once daily (QD) or placebo. The incidence of VTE was reduced from 4.96% (placebo group) to 2.77% (dalteparin group), P=0.0015 [12].

The 9th American College of Chest Physicians' (ACCP) guidelines recommend the use of heparin to combat VTE in ICU patients [13]. To analyse clinical outcomes with LMWH for thromboprophylaxis in ICU patients we searched PubMed and the Cochrane Library (up to May 2013). The following text words were used: heparin, the names of individual low-molecular-weight heparins, and critically ill patients. A total of 417 studies were identified, 35 of which pertained to chemical thromboprophylaxis in adult medical or surgical ICU patients. Based on the following criteria: 1) design: randomised controlled trials (RCTs) and 2) comparison of LMWH thromboprophylaxis with either UFH or no prophylaxis there were only 7 studies eligible for inclusion, and these are presented in Table 1. We excluded study designs that were retrospective, case reports, prospective cohort or case controlled, pilot trials, and reviews. Finally, we excluded studies published in languages other than English. Despite ICU patients receiving recommended doses of prophylactic LMWH, 5-15.5% developed proximal leg DVT in studies conducted by Fraisse et al and Cook et al. [6,14]. There was no significant increase in bleeding with the use of LMWH. The lower anti-factor Xa (anti-Xa) activity associated with standard dose LMWH may account for the occurrence of VTE despite thromboprophylaxis in ICU patients.

The effect of LMWH on the coagulation cascade is determined by anti-Xa levels [15]. Peak concentration of anti-Xa activity occurs at 3 to 4 hours after sc enoxaparin injection [16,17]. Anti-Xa levels between 0.1 and 0.3 IU/ml are considered to represent effective antithrombotic activity [18-20], and have been proposed for the medico-surgical population. Corresponding levels for ICU patients are unknown, but are thought to be higher. The European standard dose of LMWH has consistently resulted in sub-therapeutic anti-Xa activity in ICU patients [18,21,22]. Theories to explain this apparent heparin resistance include impaired absorption of sc LMWH through adrenergic mediated vasoconstriction of peripheral blood vessels [16,18,19,23] or through the presence of sc oedema. In a recent study, we showed that a weight-based dose of enoxaparin yielded satisfactory levels of anti-Xa for ICU patients, was more likely to maintain anti-Xa levels within the therapeutic range for longer periods of time, and did not result in bioaccumulation [24].

3. AN OLD FRIEND AND SOME NEW FACES

As the ACCP guidelines recommend *either* LMWH *or* unfractionated heparin (UFH) for thromboprophylaxis in ICU patients, we wanted to analyse the clinical outcomes with UFH versus LMWH. To that end, we reviewed all the RCTs generated by our previous search. Only three RCTs have compared the use of UHF and LMWH in ICU patients (Table 2).

The XPRESS study [4] conducted in patients with severe sepsis found that the rate of VTE did not vary based on the type of heparin administered. Another study comparing sc LMWH 40 mg QD with 5000 IU UFH twice daily (BID) in ICU patients undergoing major surgery found similar efficacy of UFH as compared with LMWH in the prophylaxis of DVT. Haemorrhagic complications were significantly more in the UFH group as compared with the LMWH group [25]. Cook et al recently compared UFH to LMWH in a large multicentre study. The investigators found no significant difference in the rate of proximal leg DVT between the two groups. However the proportion of patients with pulmonary emboli was significantly lower in the group that received LMWH than in the group receiving UFH [6].

LMWH has a greater than 90% bioavailability after sc administration and a plasma half-life 2 to 4 times longer than that of UFH[17]. In addition, the incidence of heparin-induced thrombocytopenia (HIT) is significantly greater among patients receiving prophylaxis with UFH compared with those receiving LMWH. Protamine sulphate neutralises 100% of the anti-Xa activity of UFH and 60% of the anti-Xa activity of LMWH [26].

Table 1. RCTs of LMWH for venous thromboembolism prophylaxis in ICU patients

Study	Population	Patients	Outcomes
Fraisse et al. Am J Respir Crit Care Med 2000 [14]	Medical ICU patients	Nadroparin N = 108 Placebo N= 113	VTE: 15.5% Nadroparin 28.2% Placebo (P =.045) Bleeding: 5.6% Nadroparin 2.7% Placebo (P = .28)
XPRESS Shorr et al. Thromb Haemost 2009 [4]	Patients with severe sepsis receiving drotrecogin alfa (activated)	Enoxaparin 40 mg QD N=478 UFH 5000 IU BID N= 498 Placebo N= 959	Symptomatic lower extremity DVT: 4.9% Enoxaparin 5.6% UFH 5.5% Placebo (P = reported as not significant)
Robinson et al. Critical Care 2010 [22]	Medico-surgical ICU patients	Enoxaparin 40 mg QD N = 18 Enoxaparin 50 mg QD N = 16 Enoxaparin 60 mg QD N= 20 Enoxaparin 70 mg QD N= 18	Peak anti-Xa levels: 0.13 IU/ml & 0.14 IU/ml for enoxaparin 40 mg QD and 50 mg QD respectively 0.27 IU/ml & 0.29 IU/ml for 60 mg QD and 70 mg QD respectively (P =.002)
De A et al. Blood Coagul Fibrinolysis 2010 [25]	Critically ill patients undergoing major surgery	Enoxaparin 40 mg QD N=81 UFH 5000 IU BID N=75	DVT incidence: 1.23% Enoxaparin 2.66% UFH (P=.51) Major bleeding : 1% Enoxaparin 2% UFH (P=.48)

PROTECT Cook et al. N Engl J Med 2011 [6]	Critically ill patients	Dalteparin 5000 IU QD N = 1873 UFH 5000 IU BID N = 1873	Proximal leg DVT: 5.1% Dalteparin 5.8% UFH (P=.57) Pulmonary emboli: 1.3% Dalteparin 2.3% UFH (P=.01) Major bleeding : 5.5% Dalteparin 5.6% UFH (P=.98)
Robinson et al. Critical Care 2013 [24]	Medico-surgical ICU patients	Enoxaparin 40 mg QD N = 20 Enoxaparin 30 mg BID N = 20 Enoxaparin 40 mg BID N= 19 Enoxaparin 1 mg/kg QD N= 19	Peak anti-Xa levels at steady state: 0.13 IU/ml & 0.15 IU/ml for enoxaparin 40 mg QD and 30 mg BID respectively 0.33 IU/ml & 0.40 IU/ml for enoxaparin 40 mg BID and 1 mg/kg QD respectively (P <.0001)
Saxena et al. J Nat Sci Biol Med 2013 [38]	ICU patients	Enoxaparin 0.6–0.8 mg/kg BID N=12 Dalteparin 125–250 units/kg QD N=12 No prophylaxis N= 12	Major bleeding : No significant difference between groups (P ≥ .05)

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; QD = once daily; BID = twice daily; N = number; DVT = deep-vein thrombosis; intensive care unit (ICU); anti-Xa= anti-factor Xa; RCTs= randomised controlled trials

Table 2. LMWH versus UFH for venous thromboembolism prophylaxis in ICU patients

Study	**XPRESS** **Shorr et al. Thromb Haemost 2009 [4]**	**De A et al.** **Blood Coagul Fibrinolysis 2010 [25]**	**PROTECT** **Cook D et al.** **N Engl J Med 2011 [6]**
Population	Patients with severe sepsis receiving drotrecogin alfa (activated)	Critically ill patients undergoing major surgery	Critically ill patients
Patient allocation	Enoxaparin 40 mg QD N=478 UFH 5000 IU BID N= 498 Placebo N= 959	Enoxaparin 40 mg QD N=81 UFH 5000 IU BID N=75	Dalteparin 5000 IU QD N = 1873 UFH 5000 IU BID N = 1873
Venous thromboembolism	Symptomatic lower extremity DVT: 4.9% Enoxaparin 5.6% UFH 5.5% Placebo (P = reported as not significant)	DVT : 1.23% Enoxaparin 2.66% UFH (P=.51)	Proximal leg DVT: 5.1% Dalteparin 5.8% UFH (P=.57) Pulmonary emboli: 1.3% Dalteparin 2.3% UFH (P=.01)
Bleeding	Not reported	Major bleeding : 1% Enoxaparin 2% UFH (P=.48) Minor bleeding : 7% Enoxaparin 16% UFH (P=.02)	Major bleeding : 5.5% Dalteparin 5.6% UFH (P=.98)

LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; QD = once daily; BID = twice daily; N = number; DVT = deep-vein thrombosis; intensive care unit (ICU)

The low intra-patient and inter-patient variability in LMWH pharmacokinetic as compared to that of UFH largely negates the need for monitoring. However periodic monitoring of anti-Xa levels is recommended in special populations, for example - pregnant patients, children, patients with acute kidney injury (AKI), or those at extremes of body weight [27]. Widespread adoption of this assay has been hampered by the cost, relative complexity, and a dearth of suitably sized studies linking clinical outcome to anti-Xa levels.

The activated partial thromboplastin time (aPTT) is most frequently used to monitor UFH because of its widespread accessibility, ease of performance, and low cost. However the test does not necessarily reflect the therapeutic effect of UFH, and suffers from additional drawbacks such as a variation in the sensitivities of different aPTT reagents, and undue influence from factors unrelated to the heparin effect. Thus there are many that advocate the use of anti-Xa levels to monitor UFH activity [28].

New drugs have recently won approval for thromboprophylaxis amongst certain patient populations. Apixaban and rivaroxaban are anticoagulants that specifically inhibit factor Xa; dabigatran etexilate is an anticoagulant that specifically inhibits thrombin. These agents can be given orally, and it is purported that no laboratory monitoring is needed. Studies have shown these agents to be more efficacious than, and just as safe as LMWH, when used in patients undergoing elective orthopaedic procedures. However they were non-superior to LMWH when used in medically ill patients, and resulted in significantly more major bleeding events [29-31]. In addition, these drugs depend on renal elimination, and a dose reduction is necessary in patients with impaired renal function [32]. LMWH also depend on renal excretion, but recent studies continue to question the need for dose adjustment. The rate of major bleeding in patients with severe renal insufficiency (creatinine clearance <30 ml/min) was similar for UFH and LMWH, and lower doses of LMWH were not correlated with decreased mortality in these patients [33].The latter findings, coupled with the additional expense incurred, absence of specific antidotes and lack of clinical experience to guide the management of major bleeding in patients taking these new peroral agents [32] ensures the continuing place of LMWH as the primary agent against VTE in ICU patients.

4. LIMITATIONS OF LMWH

Use of LMWH is contraindicated in patients with a previous history of HIT, and is not recommended for patients who are actively bleeding, or at high risk for major bleeding. In addition, despite some studies showing no increased risk of bleeding in patients with severe renal insufficiency, only one type of LMWH (dalteparin) has won approval for use in such patients [34]. Another limitation of LMWH is the cost in comparison with UFH. Finally, differences in pharmacokinetic properties and anticoagulant profiles prevent LMWH from being clinically interchangeable, and this complicates the application of results of meta-analyses [35].

5. MECHANICAL DEVICES

The ACCP guidelines also recommend the use of mechanical thromboprophylaxis with intermittent compression devices or graduated compression stockings in patients with a high bleeding risk or contraindications to heparin [12]. The theorised mechanism of action of mechanical prophylaxis is decreased venous stasis [13,36]. Compression aids are attractive adjuvants due to the lack of bleeding risk, but do not negate the need for chemical prophylaxis. They are contraindicated in patients with trauma, infection of the lower limbs, and peripheral arterial disease. The LIFENOX trial found that the use of LMWH coupled with graduated compression stockings in acutely ill medical patients, did not reduce the rate of death from any cause, as compared with graduated compression stockings alone. Pharmacologic prophylaxis with LMWH was not associated with increased rates of major bleeding [37]. The investigators did not screen for asymptomatic DVT however, and so no conclusion about the incidence of VTE between the two groups could be derived.

6. THE CHALLENGE OF MEETING THE NEEDS OF ICU PATIENTS

There is a need for consensus guidelines that encompass all the different patient groups present on the modern multidisciplinary ICU. Of the few RCTs available, disparities in ICU population and LMWH types (enoxaparin, dalteparin, nadroparin) combine to complicate pooling of these data. Further randomised double blinded controlled studies are needed, with clinical endpoints such as the occurrence of VTE and bleeding, hospital length of stay, number of ventilator free days, and mortality. Such studies should endeavour to include patients with AKI, as this is a group that has been systematically excluded from most studies; trial investigators often deeming them as too challenging.

7. UTILITY OF THE PAPER

This paper puts into perspective the range of possibilities available for thromboprophylaxis in ICU patients, and makes a strong argument for the continued use of LMWH.

8. CONCLUSION

LMWH remains a viable option for thromboprophylaxis in ICU patients, and there is reason to believe that the tide is once again turning in its favour. The heterogeneity in this patient population poses a challenge in establishing the dose of LMWH needed to provide optimal prophylaxis against VTE. Further trials, with endpoints as outlined above are needed. One such trial is currently underway at three ICUs across Denmark.

KEY POINTS:

- ICU patients are predisposed to bleeding and venous thromboembolism.
- LMWH is an excellent option for thromboprophylaxis.
- More studies are needed to assist in establishing a strategy for thromboprophylaxis.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

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COMPETING INTERESTS

The authors declare that they have no conflicts of interest.

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