



ROLE OF THROMBOPROPHYLAXIS IN CRITICALLY ILL PATIENT

Anaesthesiology

Dr. Surinder Singh Sodhi DNB, Senior Resident, Deptt. Of Anaesthesia And Surgical Intensive Care Max Superspeciality Hospital Shalimar Bagh New Delhi India 110088

Dr. Vinod Kumar Jaiswal Senior Medical Officerdeptt. Of Nephrology Max Superspeciality Hospital Shalimar Baghnew Delhi India 110088

ABSTRACT

Thromboembolism is a major complication in hospitalized patients. Intensive care unit (ICU) patients have a greater risk of thrombotic events due to additional risk factors such as immobilization, mechanical ventilation, and central catheters. The diagnosis and management of deep vein thrombosis (DVT) and pulmonary embolism (PE) in critically ill patients are challenging and these conditions are associated with high mortality. Medical thromboprophylaxis with low molecular weight heparin (LMWH) as well as unfractionated heparin (UFH) has been shown to reduce the incidence of thromboembolic events in such patients. For patients with high risk of bleeding, mechanical thromboprophylaxis can be used. The following review summarizes the existing data regarding thromboprophylaxis in ICU patients with special consideration to the use of mechanical prophylaxis and pharmacologic prophylaxis using heparin products.

KEYWORDS

INTRODUCTION

Venous thromboembolism (VTE) is a condition that involves the formation of clots in the deep veins, particularly in the veins of the lower limb. This causes obstruction to blood flow resulting in symptoms like pain, swelling and discoloration [1]. The most common complication of venous thrombosis is the migration of these clots into other blood vessels, called embolism, particularly pulmonary embolism. According to research, half of the hospitalized patients are at a risk of thromboembolism. The rate of VTE ranges from 10% to 80% percent in patients, who are not being given any prophylaxis. Studies have proven the rate of VTE is greater in hospitalized than community patients. Venous thromboembolism (VTE) in critically ill patients may be a life-threatening complication increasing duration of mechanical ventilation and stay in the intensive care unit (ICU). Both early diagnosis and effective and safe thromboprophylaxis are, therefore, daily challenges. Despite its major clinical impact, the risk of VTE in ICU has long been poorly characterised (Suppl. Figure 1), and high-quality evidence comparing pharmacologic and mechanical VTE prophylaxis strategies is still limited. Although the anticoagulant effect of heparin was elucidated in 1939, it only became used from the 1950s to prevent VTE in post-surgical patients. In 1960, a landmark trial established heparin to be effective in reducing mortality from pulmonary embolism (PE), as only surgical options were considered previously [1]. Low-molecular-weight heparin (LMWH) was discovered in the 1980s and improved thromboprophylaxis through more consistent pharmacokinetics/pharmacodynamic, simplified dosing, reduced bleeding, and less frequent heparin-induced thrombocytopenia than with unfractionated heparin (UFH) [2].

Which pharmacological thromboprophylaxis for critically ill patients?

With regard to type of prophylaxis, LMWH might have superior efficacy compared to UFH in medical and surgical critically ill patients. PROTECT [3] is the largest RCT to date to compare LMWH (dalteparin, 5000 IU/day) and UFH (5000 IU/12 h) in 3764 critically ill patients, of whom 90% were mechanically ventilated. Patients at very high risk of bleeding were excluded. Dalteparin did not decrease the rate of proximal deep vein thrombosis (DVT) compared to UFH, but the rate of PE was significantly lower with dalteparin (1.3% vs. 2.3%) (HR 0.51; 95% CI 0.30–0.88; $p=0.01$), without difference in major bleeding or in-hospital death. Also, LMWH was more effective than low-dose heparin in preventing VTE after major trauma [4].

In a recent systematic review including 13 randomised controlled trials (RCTs) (9619 critically ill patients) and comparing the efficacy and safety of thromboprophylaxis in ICU, the authors showed with a moderate certainty that LMWH reduced the rate of DVT compared to UFH (OR 0.72 [95% CI 0.46–0.98]) and with a high certainty that it reduced the rate of DVT compared to control (OR 0.59 [95% CrI: 0.33–0.90]; high certainty), while UFH may reduce DVT compared to

control (OR 0.82 [95% CrI: 0.47–1.37]) with a low certainty of evidence [5]. In this meta-analysis, the effect of LMWH compared to UFH on PE is uncertain, because of very low-quality of evidence.

Consistent with clinical studies which seem to provide a superior efficacy of LMWH compared to UFH, without an increase in bleeding complications, the European and American guidelines [2, 6] recommend pharmacological prophylaxis with LMWH over UFH in critically ill patients (Grade 1B) (Fig. 1). For patients with severe renal insufficiency, the guidelines suggest the use of UFH (Grade 2C), dalteparin (Grade 2B) or reduced doses of enoxaparin (Grade 2C) and monitoring of anti-Xa activity (Grade 2C). The guidelines also suggest no prophylaxis or the use of intermittent pneumatic compression in patients with a platelet count less than 50,000/mm³ or a high risk of bleeding (Grade 2C) and the careful use of pharmacological prophylaxis in patients with severe liver failure.

Mechanical thromboprophylaxis in critically ill patients

The place of mechanical thromboprophylaxis is still debated [5]. In the PREVENT trial [7], the use of adjunctive compression devices in addition to pharmacologic prophylaxis did not result in a reduction in DVT compared to pharmacologic prophylaxis alone. Consistently, the aforementioned meta-analysis [5] showed that compressive devices might reduce the risk of DVT compared to a control group made of a composite of no prophylaxis, placebo, or compression stockings only (OR 0.85 [95% CrI: 0.50–1.50]), although certainty evidence was low.

The European guidelines recommend against the use of graduated compression stockings alone without pharmacological thromboprophylaxis for prevention of VTE in patients at intermediate and high risk (Grade 1B) [6,8]. They recommend the use of mechanical prophylaxis for patients with contraindications for anticoagulation (Grade 1B) or in selected patients at very high risk of VTE prophylaxis in addition to pharmacological prophylaxis (Grade 2B), and suggest the use of intermittent pneumatic compression over graduated compression stockings (GCS, Grade 2B). The American guidelines do not support the use of combination therapy over either pharmacologic therapy or compression therapy alone [2].

Important considerations and pending questions

Even if these recommendations are clear, there are still several considerations that need to be taken into account for critically ill patients.

Although the availability of high-resolution reliable imaging allowed a more acute awareness for VTE over the past decades, compliance with VTE prophylaxis should still be improved. In a recent retrospective analysis of more than 1.4 million critically ill patients, 4% of patients did not receive any form of thromboprophylaxis within the first 24 h after ICU admission without obvious reason [9]. This, together with pharmacological thromboprophylaxis being often withheld in ICU due

to complications or surgical/invasive procedures, leading to less efficient thromboprophylaxis. Also, as risk factors for thromboprophylaxis failure include an elevated BMI, a personal/ family history of VTE, or vasopressor use, it is likely that more aggressive and multimodal strategies should be used in some at-risk patients [10], maybe including mechanical thromboprophylaxis.

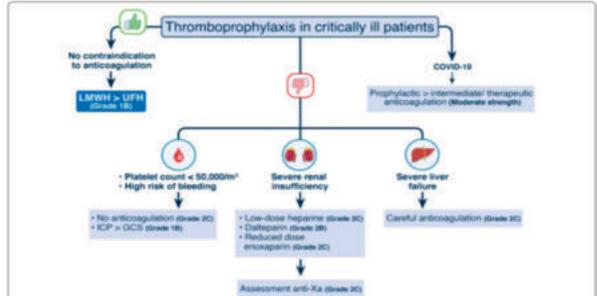


Fig. 1 Thromboprophylaxis in the critically ill. Grading of the recommendations are based on the European guidelines on perioperative venous thromboembolism prophylaxis in Intensive Care [2] and on mechanical thromboprophylaxis [8], and on the most recent guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19 from the International Society of Thrombosis and Haemostasis (ISTH) [13]. COVID-19 coronavirus disease 2019, GCS graduated compression stockings, HIT heparin-induced thrombocytopenia, IC Interimist Pneumatic Compression, LMWH low molecular weight heparin, RCT randomized controlled trials, UFH unfractionated heparin

Then, anti-factor Xa thresholds protective of VTE are still a matter of debate in critically ill patients receiving prophylactic LMWH, and personalising thromboprophylaxis to decrease adverse events in this specific population not only at high risk of VTE, but also at high risk of bleeding complications, would need an alternative anticoagulation monitoring technique [11, 12]. In this line, when a targeted level of anticoagulation is not achieved in response to heparin dose increase, heparin resistance might be invoked. The hyper coagulability of critical illness, as described for example in SARS-CoV-2 or other acute infections, might be responsible for elevated factor VIII and fibrinogen levels leading to shortened aPTT, and binding of heparin to acute-phase inflammatory proteins that decreases its effects.

This leads us to consider the question of a possible specific thromboprophylaxis regimen in critically ill patients with coronavirus disease 2019 (COVID-19), who have early been identified at increased risk of thrombotic events [14]. Consistent with several negative RCTs, the most recent guidelines from the International Society of Thrombosis and Haemostasis (ISTH) recommend using prophylactic-over the rapapeutic- or intermediate intensity anticoagulation to reduce risk of adverse events, including mortality and thromboembolism (moderate strength of recommendation, level of evidence B-Randomized RCTs) [15].

Take-home message

Considering the high risk of thrombosis in critically ill patients, general consensus currently establishes use of some form of heparin in pharmacological prophylaxis at the time of ICU admission, or mechanical thromboprophylaxis in those with contraindications to pharmacological thromboprophylaxis. LMWH is preferred over UFH for VTE prophylaxis in the ICU, unless in patients with severe renal insufficiency, where the use of low-dose heparin, dalteparin or reduced doses of enoxaparin might be preferred.

REFERENCES

1. Barritt DW, Jordan S C (1 9 6 0) Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet* 1:1309–1312
2. Schunemann HJ, Cushman M, Burnett AE, Kahn SR, Beyer-Westendorf J, Spencer FA, Rezende SM, Zakai NA, Bauer KA, Dentali F, Lansing J, Balduzzi S, Darzi A, Morgano GP, Neumann I, Nieuwlaat R, Yepes-Nunez JJ, Zhang Y, Wiercioch W (2018) American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. *Blood Adv* 2:3198–3225
3. Group PIfIcCCT, the A, New Zealand Intensive Care Society Clinical Trials G, Cook D, Meade M, Guyatt G, Walter S, Heels-Ansdell D, Warkentin TE, Zytaruk N, Crowther M, Geerts W, Cooper DJ, Vallance S, Qushmaq I, Rocha M, Berwanger O, Vlahakis NE (2011) Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med* 364:1305–1314
4. Geerts WH, Jay RM, Code KI, Chen E, Szalai JP, Saibil EA, Hamilton PA (1996) A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med* 335:701–707
5. Fernando SM, Tran A, Cheng W, Sadeghirad B, Arabi YM, Cook DJ, Moller MH, Mehta S, Fowler RA, Burns KEA, Wells PS, Carrier M, Crowther MA, Scales DC, English SW, Kyeremanteng K, Kanji S, Kho ME, Rochwerg B (2022) VTE prophylaxis in critically ill adults: a systematic review and network meta-analysis. *Chest* 161:418–428
6. Durantau J, Taccone FS, Verhamme P, Ageno W, Force EVGT (2018) European guidelines on perioperative venous thromboembolism prophylaxis: intensive care. *Eur J Anaesthesiol* 35:142–146
7. Arabi YM, Al-Hameed F, Burns KEA, Mehta S, Alsolamy SJ, Alshahrani MS, Mandourah Y, Almekhlaf GA, Almaani M, Al Bshabshe A, Finfer S, Arshad Z, Khalid I, Mehta Y, Gaur A, Hawa H, Buscher H, Lababidi H, Al Aithan A, Abdulkhalil SAI, Jose J, Afesh LY, Al-Dawood A, Saudi Critical Care Trials G (2019) Adjunctive intermittent pneumatic compression for venous thromboprophylaxis. *N Engl J Med* 380:1305–1315

8. Afshari A, Fenger-Eriksen C, Monreal M, Verhamme P, Force EVGT (2018) .Europe angulidelines on perioperative venous thromboembolism prophylaxis: mechanical prophylaxis. *Eur J Anaesthesiol* 35:112–115
9. Sahle BW, Pilcher D, Peter K, McFadyen JD, Bucknall T (2022) Trends and risk factors for omission of early thromboprophylaxis in Australian and New Zealand ICUs between 2009 and 2020. *Intensive Care Med* 48:590–598
10. Lim W, Meade M, Lauzier F, Zarychanski R, Mehta S, Lamontagne F, Dodek P, McIntyre L, Hall R, Heels-Ansdell D, Fowler R, Pai M, Guyatt G, Crowther MA, Warkentin TE, Devereaux PJ, Walter SD, Muscedere J, Herridge M, Turgeon AF, Geerts W, Finfer S, Jacka M, Berwanger O, Ostermann M, Qushmaq I, Friedrich JO, Cook DJ, Investigators PRITCCT, (2015) Failure of anti coagulant thromboprophylaxis: risk factors in medical-surgical critically ill patients*. *Crit Care Med* 43:401–410.
11. Gratz J, Wiegele M, Dibiasi C, Schaden E (2022) The challenge of pharmacological thromboprophylaxis in ICU patients: anti- FXa activity does not constitute a simple solution. *Intensive Care Med*. <https://doi.org/10.1007/s00134-022-06744-8>
12. Hofmaenner DA, Singer M (2022) The challenge of pharmacological thromboprophylaxis in ICU patients: anti- FXa activity does not constitute the simple solution. Author's reply. *Intensive Care Med*. <https://doi.org/10.1007/s00134-022-06744-8>
13. Levy JH, Connors JM (2021) Heparin resistance—clinical perspectives and management strategies. *N Engl J Med* 385:826–832
14. Helms J, Severac F, Merdji H, Anglés- Cano E, Meziani F (2020) Prothrombotic phenotype in COVID-19 severe patients. *Intensive Care Med* 46:1502–1503
15. Schulman S, Sholzberg M, Spyropoulos AC, Zarychanski R, Resnick HE, Bradbury C, Broxmeyer L, Connors JM, Falanga A, Iba T, Kaatz S, Levy J, Middeldorp S, Minichiello TA, Ramacciotti E, Samama M, Thachil J (2022) ISTH guidelines for antithrombotic treatment in COVID-19. *J Thromb Haemost*. <https://doi.org/10.1111/jth.15808>