Submitted April 2019; Accepted May 2020

ORIGINAL ARTICLE

Appropriateness of the venous thromboembolism protocol in critically ill medical patients: A cross-sectional study in a resource-limited setting

E. Hosseini[1], H. Karimpour[2], F. Shahbazi[1]

[1]Pharmaceutical Sciences Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran

[2]Department of Anesthesia, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

Correspondence

F. Shahbazi - foroud08@gmail.com

Keywords - **pharmacologic VTE prophylaxis, appropriateness, critically ill, heparin, enoxaparin**

Abstract

Background: Venous thromboembolism (VTE) is a leading cause of mortality in critically ill patients. Pharmacological thromboembolism prophylaxis is an effective way to prevent thrombosis.

Methods: A Padua risk assessment model was used to determine critically ill medical patients' risk and the appropriateness of pharmacological prophylaxis.

Results: Our analysis included 139 patients. VTE prophylaxis was considered appropriate for 89.9% of the patients who received prophylaxis. Non-guideline-approved dosing of heparin was observed in 24.4% of patients. Despite having an indication, 12.8% of patients did not receive prophylaxis. Intravenous prophylaxis was used in 6.6 % of heparin receivers. Thrombosis occurred in 2.6% of all patients.

Conclusion: Although most patients received pharmacological VTE prophylaxis, inappropriate dosing of heparin and delays in appropriate pharmacological VTE prophylaxis were common for patients with cerebrovascular disease and tumours.

Background

Venous thromboembolism (VTE) – also known as deep vein thrombosis, pulmonary thromboembolism, and distal superficial vein thrombosis – occurs in critically ill patients and is associated with longer hospital stays and increased risk of morbidity and mortality.[1] Of critically ill patients who are not on suitable prophylaxis, 13 to 31% and 0.8 to 2.3% may experience deep vein thrombosis and pulmonary thromboembolism respectively.[2] Cook et al. reported a VTE incidence rate of 2.7% in medical-surgical critically ill patients.[3] In an Iranian survey, deep vein thrombosis was reported in 3.5% of critically ill patients.[4]

Immobility for more than 72 hours, mechanical ventilation, endothelium injury, recent surgery, pregnancy, obesity, active cancer, chemotherapy, stroke, and central catheter are among the known risk factors associated with thrombosis in critically ill patients.[5] The American College of Physicians recommends that VTE prophylaxis should be performed for at-risk acutely ill patients.[6] Placebo-controlled studies have shown that unfractionated heparin, low-molecular-weight heparin, and fondaparinux are effective for VTE prevention.[2,7] Heparin and low-molecular-weight heparin have similar levels of efficacy in non-traumatic patients.[8] However, for treating trauma patients, low-molecular-weight heparin is more favourable than heparin.[9]

Several risk assessment models, including the Caprini, Padua, Geneva, and Kucher models, have been employed to predict VTE risk.[10] The authors who originally proposed the Padua score categorised patients as either low-risk (score <4) or high-risk (score ≥4) based on information related to 11 common VTE risk factors.[11] About 40% of 1180 patients who were high-risk. VTE occurred in 11% of high-risk patients and only 0.3% of low-risk patients.[11]

These risk assessment methods have been validated in subsequent studies.[12,13] Among these methods, the Padua risk assessment model has been identified as the best for predicting thrombotic and haemorrhagic risk among hospitalised medical patients.[14] A recent systematic review highlighted that only the Padua VTE risk assessment models and the IMPROVE VTE have been validated for risk assessment among hospitalised acutely ill medical patients.[15] Finally, recent guidelines given by the American Society of Hematology mentioned the Padua and IMPROVE scores as the two most extensively used risk scores for assessing critically ill medical patients.[16]

The aim of the current study is to determine the appropriateness of using VTE prophylaxis regimens according to the Padua risk assessment model in critically ill medical patients.

Procedure

The study protocol was approved by the ethical committee of Kermanshah University of Medical Sciences, Kermanshah,

Table 1. Padua score

Risk factor	Points
Active cancer	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility	3
Already known thrombophilic condition	3
Recent (≤1 month) trauma and/or surgery	2
Age ≥70 years	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischaemic stroke	1
Acute infection or rheumatological disorder	1
Body mass index ≥30	1
Ongoing hormonal treatment	1

Iran. The study conducted in the intensive care unit of Imam Reza Hospital. All medically ill patients who were admitted to the general intensive care unit and remained there for at least 72 hours were included in our survey. Patients who underwent surgery, experienced active bleeding, had a platelet count of less than 50,000/mm^3, or received therapeutic doses of anticoagulants were excluded from this survey.

Padua scores were used to predict deep vein thrombosis risk *(table 1)*. Heparin (at a dose of 5000-7500 units twice to thrice daily) and enoxaparin (30-40 mg daily according to the renal function and 30-40 mg twice daily for obese patients) are two commonly used anticoagulants in our hospital's pharmacopeia. For the abovementioned patients, mechanical prophylaxis (thromboembolic deterrent stockings and intermittent pneumatic compression devices) was considered. Patients were also followed for possible adverse effects. Serum creatinine, creatinine clearance, sequential organ failure assessment, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, and platelet count were recorded for each patient. Patients who were included in the survey were assessed at least every other day, and changes (such as discontinuation of or changes to their prophylaxis regimen) were made.

Table 2. Baseline characteristics of patients received VTE prophylaxis

	Heparin	Enoxaparin	p-value
Mean age (years)	67.23±13.92	55.75±17.48	0.002
Sex (male)	26/43 (60.5%)	37/66 (56%)	0.69
Mean serum creatinine (mg/dl)	1.72±1.5	1.12±0.69	0.082
Platelet count (/mm3)	194.6±86.48	224.95±100.51	0.052
Creatinine clearance (ml/min)	58.53±34.24	85.02±39.34	0.001
INR	1.24±0.5	1.14±0.3	0.08
SOFA	4 (1-9)	3 (0-14)	0.16
APACHE II	14 (5-26)	9.5 (0-24)	<0.001

The primary purpose of our study is to evaluate the appropriateness of VTE prophylaxis protocols among critically ill patients (i.e., those with a Padua score of 4 or more). Risk scores were calculated by one researcher (E.H), and the intensivist was unaware of patients' risk levels.

SPSS version 16 was used for data analysis. A chi-square test was used to determine the sex distribution between heparin and enoxaparin groups. Finally, a Wilcoxon test was used for quantitative data analysis.

Results

The study took place over one year, from April 2017 to April 2018. During this time, 450 patients were admitted to our wards, and 150 medically ill patients who were hospitalised for more than 72 hours were included in our survey. Of the 150 patients, 139 (92.6%), with a mean age of 58±18 years, met our criteria. Central nervous system complications (ischaemic and haemorrhagic stroke, and brain tumours) were the leading reason for admission (56/150, 37%), followed by pneumonia (30/150, 20%), acute COPD exacerbation (14/150, 9.3%), HELLP syndrome (7/150, 4.6%), intra-abdominal infections (5/150, 3.3%), and lupus erythematosus (5/150, 3.3%). Sepsis was diagnosed in 52.6% of the patients during their ICU stay.

The mean ICU stay was 17.28±1.81 days. The baseline characteristics of the patients are shown in *table 2*. The median APACHE II score was significantly higher in heparin receivers (p<0.001) than in non-receivers. Also, mean creatinine clearance was significantly higher in enoxaparin receivers than in non-receivers.

Ninety percent (125/139, 89.9%) of patients were candidates for VTE prophylaxis, and 109 of these 125 patients (87.2%) received prophylaxis. Most candidates (51.2%) received enoxaparin, followed by unfractionated heparin (36%). Padua scores were significantly higher in heparin receivers than in non-receivers *(table 3)*. Only six of those who were not VTE prophylaxis candidates did not receive prophylaxis. In addition, 14 of the 125 (11.2%) VTE prophylaxis candidates did not receive the appropriate pharmacological prophylaxis *(table 4)*. Enoxaparin dose and route of administration were similar in all receivers (64/125, 51.2%). However, among patients who received heparin prophylaxis, 17.8% (8/45) received only 5000 units of heparin per day, and 6.6% (3/45) of them received a prophylactic dose of heparin intravenously (12,500 units/day, or 500 units per hour). Furthermore, despite showing no sign of new haemorrhages on control computed tomography, 16/125 patients (12.8%) of candidates did not receive VTE prophylaxis. In other words, 28.5% (16/56) of patients with central nervous system complications did not receive VTE prophylaxis. Intracranial haemorrhage (7/16) and brain tumours (5/16) were the main reasons for the delayed initiation of VTE prophylaxis. In these patients, graduated compression stockings were used.

Older patients with renal failure and high APACHE II scores

Table 3. Padua score results

Mean score	7(0-16)
VTE prophylaxis type* • Enoxaparin • Heparin	 6 (4-15) 8 (4-16)
VTE score • 0-3 • 4-8 • 9-12 • 13-16	 14/139 (10.1%) 83/139 (59.7%) 35/139 (25.2%) 7/139 (5%)

*significant difference

were more likely than others to receive heparin. In contrast, a high platelet count was associated with more enoxaparin use *(table 2)*.

Six patients (4/139, 2.6%) experienced confirmed lower extremity deep vein thrombosis during their ICU stay, and their prophylactic regimens were changed to intravenous heparin infusion. Unfortunately, only two patients received partial thromboplastin time directed heparin dosing, the others received only 1000 units of heparin per hour.

Eight patients (5/139, 5.7%) experienced gastrointestinal bleeding, in which case VTE prophylaxis was temporarily stopped. However, no significant associations were observed between enoxaparin and heparin administration and bleeding. Furthermore, no definite cases of heparin-associated thrombocytopenia were seen during the study, and major bleeding (e.g., gastrointestinal bleeding) occurred in eight patients.

Discussion

According to the Padua scores, nearly 90% of patients were candidates to receive VTE prophylaxis, 87.2% of whom received prophylaxis. Unfortunately, the others, despite their high VTE risk, did not receive pharmacological prophylaxis. Dosing of enoxaparin and heparin was appropriate in most candidates.

Previous studies have reported different anticoagulation appropriateness of prophylaxis in hospitalised patients.[17,18] The results of our study are similar to those of Nekoonam et al., who reported more than 88% of patients received appropriate VTE prophylaxis according to the Caprini risk assessment model.[18] Half of our VTE prophylaxis candidates received subcutaneous enoxaparin, while about two-thirds of patients received subcutaneous enoxaparin in the study by Nekoonam et al. However, they did not report the occurrence of VTE.[18]

Table 4. Appropriateness of VTE protocol

VTE prophylaxis candidate	Heparin	Enoxaparin	No pharmacological prophylaxis
Yes	45/125 (36%)	64/125 (51.2%)	16/125 (12.8%)
No	3/14 (21.4%)	5/14 (35.7%)	6/14 (42.9%)

Chaudhary et al. evaluated the appropriateness and cost-effectiveness of VTE prophylaxis in general medical wards according to Padua scores.[17] Each patient's risk was compared with the documented risk in the electronic records. Patients were categorised into four groups (low documented, low calculated risk; low documented, high calculated risk; high documented, low calculated risk; and high documented, high calculated risk). The researchers observed appropriate VTE prophylaxis use in 54.9% of acutely ill patients.[17] In addition, they showed that 12% (vs. 11% in our study) of high-risk patients without contraindication received only mechanical prophylaxis.[17]

We only calculated Padua scores. In our centre, VTE prophylaxis is universally considered for all admitted patients. As with the previously mentioned studies, a high rate of VTE prophylaxis was used in our study. However, inappropriate doses of LMWHs were common in our study.

A current guideline from the Neurocritical Care Society recommends the use of VTE prophylaxis after 72 hours in patients suffering from an intracranial haemorrhage. In our study, most VTE prophylaxis candidates who did not receive pharmacological VTE prophylaxis within 72 hours had a, spinal tumours, or intracranial haemorrhage.[19] Fear of rebleeding was the main reason for delayed prophylaxis initiation. Graduated compression stockings were used in these patients.

It has been recommended that patients with a high bleeding risk receive mechanical prophylaxis and are shifted to pharmacological prophylaxis when bleeding risks decrease. [20] However, current European and US guidelines do not recommend the use of graduated compression stockings.[21,22] In our survey, VTE prophylaxis candidates who did not receive appropriate prophylaxis were offered graduated compression stocking treatment instead of pharmacological and suitable mechanical (intermittent pneumatic compression) prophylaxis.

A small number of our patients received intravenous heparin at prophylactic doses for VTE prophylaxis, as the intravenous route may have superiority for patients suffering from septic shock. However, the appropriateness of this approach should be clarified in further clinical studies.[23] Cheng et al. evaluated coagulation status and factor Xa level after subcutaneous heparin and the infusion of heparin with a target activated partial thromboplastin time of 40-45 sec. Patients in the subcutaneous group had a hypercoagulable profile and undetectable anti-factor Xa levels.[23] However, this approach is not supported by current guidelines, and further studies are needed to better clarify the role of intravenous heparin for VTE prophylaxis.

Correct anticoagulant dosing is necessary to achieve an appropriate response. About 4% of our patients experienced lower extremities VTE. Our results are consistent with studies by Miri et al. and Cook et al., who reported VTE prevalence rates of 3.5% and 2.7%, respectively, in critically ill patients. [3,4] However, another survey from northern India showed a VTE

incidence rate of only 0.8% in medical-surgical intensive care patients.[24]

Results from a meta-analysis recommended either giving heparin doses either twice or thrice daily, but not only once.[25] In our survey, enoxaparin was prescribed more often for patients with high platelet counts and creatinine clearance and low APACHE II scores. Older patients, as well as patients with higher INR and lower kidney function, were more likely to receive heparin. This could be due to the lower risk of heparin accumulation in renal failure, lower pharmacological half-life, and, subsequently, bleeding risk in this population.[26] However, in elderly patients with normal renal function, LMWHs are the agents of choice, while the administration of unfractionated heparin may be considered for patients with a GFR ≤30 ml/min.[27]

Finally, our results show that the underutilisation of VTE prophylaxis among patients with cerebrovascular accidents and brain tumours is high. Only critically ill medical patients were included in our survey. As highlighted, universal prophylaxis was initiated for nearly all patients in our hospital, which can increase treatment-related adverse effects. Using a risk assessment model, such as the Padua model, is helpful in a resource-limited setting where bedside ultrasonography is not widely available, thus potentially increasing the appropriateness of VTE prophylaxis.

Limitations

First, diagnostic workups were only done for symptomatic patients, and we were unable to follow up with all patients regarding all possible VTE events during their hospitalisation. Second, the sample size of the current study was not large enough to evaluate the efficacy of different types of pharmacological prophylaxis.

Conclusion

The results of this study highlight the need for VTE risk assessment guides to initiate appropriate pharmacologic prophylaxis in critically ill patients.

Disclosures

All authors declare no conflict of interest. No funding or financial support was received.

References

1. Kaplan D, Casper TC, Elliott CG, et al. VTE incidence and risk factors in patients with severe sepsis and septic shock. Chest. 2015; 148:1224-30.
2. Minet C, Potton L, Bonadona A, et al. Venous thromboembolism in the ICU: main characteristics, diagnosis and thromboprophylaxis. Crit Care. 2015; 19:287.
3. Cook D, Crowther M, Meade M, et al. Deep venous thrombosis in medical-surgical critically ill patients: prevalence, incidence, and risk factors. Crit Care Med. 2005;33(7):1565-1571.
4. Miri M, Goharani R, Sistanizad M. Deep vein thrombosis among intensive care unit patients; an epidemiologic study. Emerg (Tehran). 2017;5: e13.
5. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: the Padua Prediction Score. J Thromb Haemost. 2010; 8:2450-7.
6. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ. Executive summary: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2012;141(2 Suppl):7S.
7. Cade JF. High risk of the critically ill for venous thromboembolism. Crit Care Med. 1982; 10:448-50.
8. Fraisse F, Holzapfel L, Couland J-M, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. Am J Respir Crit Care Med. 2000; 161:1109-14.
9. Geerts WH, Jay RM, Code KI, et al. A comparison of low-dose heparin with low-molecular-weight heparin as prophylaxis against venous thromboembolism after major trauma. New Engl J Med. 1996; 335:701-7.
10. Stuck AK, Spirk D, Schaudt J, Kucher N. Risk assessment models for venous thromboembolism in acutely ill medical patients. Thromb Haemost. 2017; 117:801-8.
11. Barbar S, Noventa F, Rossetto V, et al. A risk assessment model for the identification of hospitalized medical patients at risk for venous thromboembolism: The Padua Prediction Score. J Thromb Haemost. 2010; 8:2450-7.
12. Moorehead KJ, Jeffres MN, Mueller SW. A retrospective cohort analysis of pharmacologic VTE prophylaxis and Padua prediction score in hospitalized patients with chronic liver disease. J Pharm Pract. 2017; 30:58-63.
13. Saliba W, Zahalka W, Goldstein L, Ron G, Elias M. Padua prediction score and thrombin generation in hospitalized medical patients. Thromb Res 2014; 134:803-6.
14. Depietri L, Marietta M, Scarlini S, et al. Clinical impact of application of risk assessment models (Padua Prediction Score and Improve Bleeding Score) on venous thromboembolism, major hemorrhage and health expenditure associated with pharmacologic VTE prophylaxis: a "real life" prospective and retrospective observational study on patients hospitalized in a Single Internal Medicine Unit (the STIME study). Intern Emerg Med. 2018; 13:527-34.
15. Mahan CE, Fisher MD, Mills RM, et al. Thromboprophylaxis patterns, risk factors, and outcomes of care in the medically ill patient population. Thromb Res. 2013; 132:520-6.
16. Schünemann HJ, Cushman M, Burnett AE, Kahn SR, et al. American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and nonhospitalized medical patients. Blood Adv. 2018; 2(22): 3198–3225.
17. Chaudhary R, Damluji A, Batukbhai B, et al. Venous Thromboembolism Prophylaxis: Inadequate and Overprophylaxis When Comparing Perceived Versus Calculated Risk. Mayo Clinic Proceedings: Innovations, Quality & Outcomes. 2017;1(3):242-7.
18. Nekoonam B, Eshraghi A, Hajiesmaeili M, Sahraei Z. Deep Vein Thrombosis Prophylaxis Evaluation in Intensive Care Unit. Arch Crit Care Med. 2016;1(4).
19. Nyquist P, Bautista C, Jichici D, et al. Prophylaxis of venous thrombosis in neurocritical care patients: an evidence-based guideline: A Statement for Healthcare Professionals from the Neurocritical Care Society. Neurocrit Care. 2016;24(1):47-60.
20. Geerts W, Selby R. Prevention of venous thromboembolism in the ICU. Chest. 2003; 124:357S-63S.
21. Steiner T, Al-Shahi Salman R, Beer R, et al. European Stroke Organisation (ESO) guidelines for the management of spontaneous intracerebral hemorrhage. Int J Stroke. 2014; 9:840-55.
22. Hemphill III JC, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2015; 46:2032-60.
23. Cheng SS, Nordenholz K, Matero D, et al. Standard subcutaneous dosing of unfractionated heparin for venous thromboembolism prophylaxis in surgical ICU patients leads to subtherapeutic factor Xa inhibition. Intensive Care Med. 2012; 38:642-8.
24. Kumar A, Mehta Y, Ali T, Gupta MK, George JV. Deep vein thrombosis in medical and surgical intensive care unit patients in a tertiary care centre in North India: incidence and risk factors. J Anaesthesiol Clin Pharmacol. 2017; 33(2): 181–186.
25. Phung OJ, Kahn SR, Cook DJ, Murad MH. Dosing frequency of unfractionated heparin thromboprophylaxis: a meta-analysis. Chest. 2011; 140:374-81.
26. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141: e576S-e600S.
27. Dorobantu M, Bogdan S. Unfractionated heparin or low-molecular-weight heparin in the elderly. Int J Cardiol. 2016; 222:1084-90.