

Venous thromboembolism in a medical intensive care unit

The effect of implementing clinical practice guidelines

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ABSTRACT

الأهداف: تحديد معدل حدوث التجلطات الوريدية في مرضى الأمراض الباطنية الذين يتم إدخالهم إلى العناية المركزة وذلك عقب تطبيق نظام موحد للوقاية من التجلطات الوريدية باستخدام عقار الهيبارين مرتين يومياً، وكذلك للتعرف على العوامل التي تزيد من خطر الإصابة بالتجلطات الوريدية في هؤلاء المرضى.

الطريقة: أُجريت هذه الدراسة الاسترجاعية على 123 مريضاً تم تنويمهم في قسم العناية المركزة في مستشفى الملك خالد الجامعي، الرياض، المملكة العربية السعودية وذلك خلال الفترة من مارس 2010م إلى أبريل 2011م. لقد تم استثناء المرضى الذين لديهم موانع لاستخدام عقار الهيبارين، أو الذين يتلقون العقاقير المذيبة للتجلطات، ومن ثم تم إعطاء المرضى الذين ثبتت بالأشعة الصوتية للأوردة خلوصهم من التجلطات الوريدية العميقة عقار الهيبارين مرتين يومياً. جُمعت خصائص المرضى الديموغرافية والسريرية، ثم أُعيد فحص الأشعة الصوتية للأوردة مرتين أسبوعياً لمدة 6 أسابيع.

النتائج: شملت الدراسة 104 مريضاً مستوفين للشروط المطلوبة، وتم تشخيص التجلطات الوريدية العميقة في 10 مرضى منهم بينما كانوا يتلقون عقار الهيبارين أي بمعدل 9.8%، وكانت نسبة الامتثال للنظام الوقائي 98%. وقد وجد أن إلتان الدم ($p=0.0167$)، وقلة الحركة ($p<0.0001$)، وحدوث تجلطات وريدية سابقة ($p=0.024$)، والمتلازمة الكلوية ($p=0.008$) أكثر شيوعاً في المرضى الذين أصيبوا بالتجلطات عن غيرهم. إلا أن استخدام الانحدار اللوجستي أشار إلى أن الإصابة السابقة بتجلطات وريدية هو العامل الوحيد الذي يزيد من خطر الإصابة بالتجلطات الوريدية بصورة كبيرة من الناحية الإحصائية ($B=-0.439$, $AOR=5.01$, $p<0.0001$).

خاتمة: تشير هذه الدراسة إلى أن تطبيق توجيهات الممارسات السريرية لمنع التجلطات الوريدية في مرضى الباطنة المصابين بحالات حرجة باستخدام عقار الهيبارين مرتين يومياً نتج عنه زيادة في التقيد بالنظام الوقائي، وانخفاض في معدل التجلطات الوريدية. كما تبين أن المرضى الذين أصيبوا بالتجلطات الوريدية كان لديهم تاريخ مرضي بالتجلطات الوريدية أكثر من غيرهم.

Objectives: To determine the incidence of VTE in medical patients admitted to the intensive care unit (ICU) following the implementation of a standard

deep venous thrombosis (DVT) prophylaxis protocol using unfractionated heparin (UFH), and to identify risk factors for DVT in these patients.

Methods: We prospectively studied 123 consecutive patients admitted to the Medical ICU of King Khalid University Hospital, Riyadh, Saudi Arabia. We excluded patients on anticoagulation or with contraindications for heparin. Patients who were negative for DVT by screening Doppler Ultrasound (U/S) were started on UFH twice a day. The Doppler U/S was repeated twice weekly for 6 weeks.

Results: One hundred and four critically ill medical patients were included. A DVT was diagnosed in 10 patients while receiving UFH, an incidence rate of 9.8%. The compliance rate was 98%. Sepsis ($p=0.0167$), limited mobility ($p<0.0001$), previous DVT ($p=0.024$), and nephrotic syndrome ($p=0.008$) were significantly more common in patients who developed DVT compared with others. However, by backward logistic regression, previous DVT was the only significant factor for the development of DVT ($B=-0.439$, $AOR=5.01$, $p<0.0001$).

Conclusion: The implementation of clinical practice guidelines for VTE prophylaxis in critically ill medical patients using UFH twice daily resulted in a high compliance rate and low incidence of VTE. Previous DVT was a significant risk factor for development of VTE.

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Acute venous thromboembolism (VTE) is a serious and potentially lethal disease, which can significantly impair the recovery of hospitalized patients.¹ Critically ill patients have an increased risk of deep venous thrombosis (DVT) and pulmonary embolism (PE) due to the multiple VTE risk factors present prior to intensive care unit (ICU) admission, such as recent surgery, trauma, burn, sepsis, prolonged bed rest, malignancy, cardiac or respiratory failure, and stroke.²⁻⁶ In addition, other risk factors may be acquired during the ICU stay, including mechanical ventilation, central line catheters, immobility, sedatives, and paralytic agents.^{2,3,7} A recent systematic review reported that the incidence of asymptomatic VTE in critically ill patients varied from 3.7-26% (median 12.8%).⁸ Furthermore, previous studies have shown that anticoagulant prophylaxis in the ICU patients can effectively avoid both fatal PE and non-fatal VTE;⁹⁻¹¹ however, most of these studies involved a heterogeneous population of critically ill patients with short follow up and variable compliance rates. The aim of this study was to determine the incidence of VTE in critically ill medical patients after implementing a standardized DVT prophylaxis protocol of unfractionated heparin (UFH) 5000 units, subcutaneous (SC) injection twice daily (BID), and to identify the risk factors for DVT in these patients.

Methods. In this prospective study, all consecutive medical patients admitted to the medical ICU (MICU) at King Khalid University Hospital (KKUH), Riyadh, Saudi Arabia from March 2010 to April 2011 were evaluated for study eligibility. The Institutional Ethics Review Board (IRB) of the College of Medicine, King Saud University, approved the study, which was carried out according to the Principles of Helsinki Declaration involving medical research concerning human subjects, and written informed consent was obtained from all participating patients. Patients were excluded if they had DVT on admission, or who had contraindications to heparin, including known allergy to heparin, platelets <50 units, active bleeding, INR or a PTT ≥ 2 times the upper limits of normal values, or those who were on therapeutic anticoagulation for other reasons. Otherwise all admitted patients to the MICU were included

during the prescribed study period. Demographic information, diagnosis, co-morbid conditions, Acute Physiology And Chronic Health Evaluation (APACHE II) score for severity of illness, mechanical ventilation, use of central line and its site, duration of ICU stay, and outcome were collected. All patients underwent baseline assessment including medical history, physical examination, and screening of bilateral lower extremity using Doppler venous sonography. Images were obtained with compression augmentation followed by color flow, and Doppler waveforms from the common femoral vein to the popliteal trifurcation. Diagnosis of DVT was based on the presence or absence of venous flow, vein compressibility, and lack of augmentation and response to distal compression maneuver. Sonography and reading were performed by an assigned certified vascular technologist using a portable vascular ultrasound machine ATL-5000 and SonoSite Titan by using L7-5 and C5-2 MHZ frequency probes (SonoSite Inc., Bothell, WA, USA).¹² Patients' whose baseline from Doppler U/S was negative for DVT, were started on the ICU protocol for DVT prophylaxis based on the American College of Chest Physicians (ACCP) Guidelines 2007, comprising UFH 5000 units SC twice daily.² Patients were continued on prophylaxis and followed twice weekly with Doppler U/S for 6 weeks.

Before implementation of the DVT prophylaxis protocol, the ICU medical staff attended a DVT awareness and educational symposium. Compliance with the approved protocol was documented and monitored by a quality nurse using a daily checklist. The DVTs were classified as proximal (thigh veins; namely, popliteal, femoral or iliofemoral), or distal (calf veins; namely, anterior or posterior tibial or peroneal veins). If the patient developed PE during hospital stay, the diagnostic method was recorded and Doppler ultrasound was performed. During hospitalization, patients were observed for complications of pharmacological prophylaxis, including bleeding and heparin-induced thrombocytopenia (HIT). Bleeding was considered major if it resulted in hemoglobin (Hb) drop ≥ 2 g/dL, or if it was in a critical location including retroperitoneal and intracranial bleeding.

Numeric data were summarized as median, minimum, maximum, and standard deviation, and categorical data as percentages. Statistical analysis was performed using Predictive Analysis Software version 18 (PASW, IBM, Chicago, Illinois, USA). Comparison of patient characteristics, risk factors, co-morbidities between those who developed DVT and those who did not was performed using Mann-Whitney U-Test and Fisher Exact Test. A *p*-value <0.05 was considered statistically significant.

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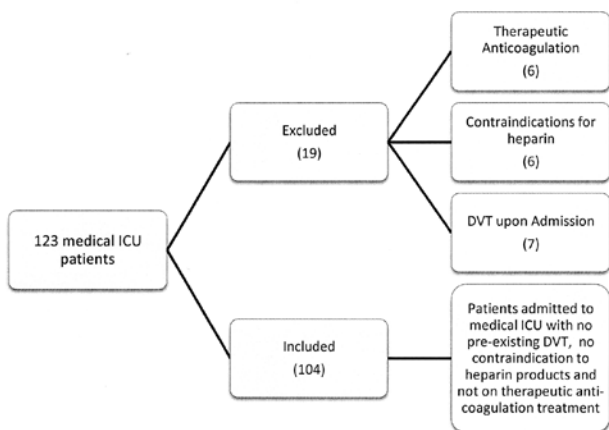


Figure 1 - Patient enrollment in the deep vein thrombosis study. ICU - intensive care unit

Results. Of 123 consecutive patients admitted to the MICU, 19 patients were excluded: 7 had DVT upon admission as detected by baseline Doppler U/S, 6 were on therapeutic anticoagulation (5 with atrial fibrillation, and one was admitted with pulmonary embolism), and 6 had contraindication for thromboprophylaxis because of bleeding, thrombocytopenia, or impaired coagulation profile (Figure 1). Of the 104 eligible patients, proximal DVT was diagnosed in 10 (9.6%): 6 had iliofemoral DVT while 4 had DVT in the femoral vein, out of which, 2 patients had concurrent distal DVT in the posterior tibial veins. A DVT was detected on day 3 after ICU admission in 2 patients, day 7 in 4, day 14 in 3, and day 35 in one patient. None of the patients developed PE during their ICU stay. Six patients were discharged home after 4 weeks and were followed up as outpatients using the same protocol. However, none of them developed DVT. More than two-thirds of patients were older than 50, and females were a little more than males (53 females, 51 males). However, significantly more patients with DVT were females. Approximately half (52%) of the patients had an admitting diagnosis of sepsis, which was present in significantly more (90%) patients with DVT ($p=0.0167$). The most common preexisting risk factors for DVT were obesity (39.4%), followed by immobility and cancer; however, significantly more patients with DVT were non-ambulatory (70%) compared with the prevalence of other risk factors ($p<0.0001$). Similarly, history of previous DVT was more frequent in patients with DVT than those without DVT ($p=0.024$). Two patients who developed DVT had nephrotic syndrome, whereas none of the other patients had this diagnosis upon admission ($p=0.008$). The most common co-morbid conditions in the study group were diabetes and hypertension followed by chronic obstructive pulmonary disease, cancer,

Table 1 - Comparison of enrolled medical ICU patients in the study who developed and did not develop DVT.

Characteristics	With DVT (n=10)	Without DVT (n=94)	P-value
	n (%)		
Age			
16-45	3 (30)	27 (28.7)	1.0
46-65	3 (30)	32 (34.1)	1.0
>65	4 (40)	35 (37.2)	1.0
Gender			
Male	2 (20)	49 (52.1)	0.09
Female	8 (80)	45 (47.9)	0.09
APACHE II score median (min-max)	20.5 (7-72)	20 (9-35)	0.356
Admitting diagnosis			
Sepsis	9 (90)	45 (47.9)	0.0167
AKI	0	13 (13.8)	0.35
Respiratory disease	1 (10)	12 (12.8)	1.0
CNS disease	2 (20)	8 (8.5)	0.24
CVS disease	1 (10)	5 (5.3)	0.46
Others	0	6 (6.4)	1.0
Preexisting risk factors for DVT			
Bedridden	7 (70)	10 (10.7)	<0.0001
Obesity	3 (30)	28 (40.4)	1.0
SLE/vasculitis	1 (10)	4 (4.3)	0.40
Previous DVT	2 (20)	1 (1.1)	0.024
Cancer	1 (10)	11 (11.7)	1.0
Nephrotic syndrome	2 (20)	0	0.008
Co-morbid conditions			
DM/HTN	2 (20)	30 (31.9)	0.72
COPD	1 (10)	19 (20.2)	0.68
CKD	1 (10)	11 (11.7)	1.0
Cancer	2 (20)	11 (11.7)	0.61
Hypothyroidism	2 (20)	9 (9.6)	0.28
Stroke	1 (10)	6 (6.4)	0.51
ICU acquired risk factor			
Mechanical ventilation	8 (80)	84 (89.4)	0.32
Inotrope	8 (80)	73 (77.7)	1.0
Central line	10 (100)	80 (85.1)	0.35
Muscle relaxant	4 (40)	55 (58.5)	0.32
Sedatives	8 (80)	77 (81.9)	0.77

DVT - deep vein thrombosis, APACHE - acute physiology and chronic health evaluation, AKI - acute kidney injury, SLE - systemic lupus erythematosus, HTN - hypertension, COPD - chronic obstructive pulmonary disease, CVS - cardiovascular system, CNS - central nervous system, RESP - respiratory, DM - diabetes mellitus, CKD - chronic kidney disease, ICU - intensive care unit

and chronic kidney disease; however, no significant difference was observed among the 2 groups. Similarly, there was no significant difference in ICU acquired DVT risk factors, including mechanical ventilation, inotropes, central line, muscle relaxants, and sedative, which were present in most of the patients (Table 1). A backward logistic regression model was constructed and significant factors including sepsis, history of previous DVT, immobility, and nephrotic syndrome were entered into the model to eliminate the possible confounding

Table 2 - Logistic regression analysis of the potentially significant risk factors for deep venous thrombosis (DVT).

Variables	B-value	P-value	Adjusted odds ratio	95% confidence interval
History of DVT	-0.439	<0.0001	5.01	2.40-7.60
Sepsis	0.045	0.785	0.67	0.13-3.6
Bedridden	-0.043	0.549	4.67	0.70-31.0
Nephrotic syndrome	-0.115	0.384	1.20	0.84-1.70

relationship among variables and indicate the variables that showed statistical significance. Only history of previous DVT was significantly correlated with the development of DVT (Table 2). Compliance with the DVT prophylaxis policy was 98%. Overall bleeding occurred in 10 patients (9.6%), out of which, 3 (2.8%) had major bleeding. The site of major bleeding was the gastrointestinal tract in 2 patients and retroperitoneal in one. Three patients developed HIT as diagnosed by enzyme-linked immunosorbent assay (ELISA);¹³ therefore, heparin was stopped and they were started on Fondaparinux as per protocol,¹⁴ however, none of them developed any thromboembolic event. The mean ICU length of stay for the patients who developed DVT was 16 days, minimum was 3 days, and maximum was 35 days. One patient died on the thirty-seventh day, while the rest of the patients survived the study period.

Discussion. In this study, we found a low incidence of VTE in critically ill medical patients using UFH 5000 units SC twice a day when a standardized protocol for DVT prophylaxis was implemented and accompanied by a high compliance rate. The incidence of VTE during ICU stay and up to 6 weeks in our study (9.6%) is similar to previous reports with this regimen,¹⁵⁻¹⁷ and comparable to that reported following prophylaxis with UFH 3 times a day or LMWH.¹⁸⁻²¹ Our findings are also in agreement with older reports that showed lower incidence with this low dose heparin (LDH) strategy.^{22,23}

In 1995, Hirsch et al,¹⁵ using Doppler U/S, reported that 33% of MICU patients developed DVT despite the use of unfractionated LDH twice a day and intermittent pneumatic compression. Similarly, Ibrahim et al¹⁷ detected DVT in 24% of patients receiving prolonged mechanical ventilation. On the other hand, 2 other randomized thromboprophylaxis trials^{16,18} comparing LDH with placebo reported a lower incidence rate of DVT (11% and 13%). Furthermore, when twice a day dosing of UFH was compared to 3 times, no significant difference was detected in VTE rate.²³ We think the low incidence in our study might be related to the higher compliance rate with the prophylaxis protocol,

facilitated by implementing proven strategies^{24,25} including staff education regarding DVT prophylaxis, followed by compliance monitoring. Our compliance rate (98%) was higher than the average compliance rate (69%) reported in previous studies in intensive care units suggesting under utilization of VTE prophylaxis in ICUs in general.²⁶

Unfractionated heparin was the pharmacological agent used in our DVT prophylaxis protocol. In a recent meta analysis of VTE prophylaxis in medically ill patients, the rates of DVT were similar when comparing LMWH with UFH (odds ratio, 0.92; 95% confidence interval, 0.56-1.52). No significant differences in PE or death were found among the UFH and LMWH groups.¹⁹ Similarly, a Cochrane Database Systematic Review conducted in 2009 showed no statistically significant difference in efficacy between LMWH and UFH.²⁰ However, as many patients are admitted to the ICU with acute kidney injury (AKI), or develop AKI during their course of illness, bioaccumulation of LMWH represented a potential risk,^{27,28} therefore, we favored the use of UFH. None of the 13 patients in our study admitted with AKI developed DVT on UFH prophylaxis.

In this study the overall frequency of bleeding was 9.6% and the rate of major bleeding was 2.8%. This is higher than previous reports for patients on UFH and LMWH.^{11,27-29} The difference could be attributed to the older age of the patients in our study, the presence of multiple co-morbid conditions, and the use of mechanical ventilation and vasopressors in over 80% of patients, which puts them at higher risk for bleeding. Heparin-induced thrombocytopenia was diagnosed in 3 patients in our study (2.9%). Previous studies in surgical patients reported the incidence of HIT with UFH to range between 1.1-3.8% with an absolute risk of 2.6%.^{30,31} Recent studies in medical patients, however, suggested lower incidence in hospitalized medical patients (0.8%), but none included ICU patients.^{29,32}

Several attempts have been made to identify risk factors for VTE in hospitalized medical patients in general and in critical care patients in particular.^{7,33,34} The major risk factors include the New York Heart Association class III and IV heart failure, COPD exacerbations, and sepsis. Additional risk factors include advanced age, history of VTE, cancer, prolonged bed rest and stroke with lower extremity weakness. In our study sepsis was the most common admitting diagnosis in patients who developed DVT. There is ample evidence drawn from many studies showing sepsis to be an important risk factor for VTE in critically ill patients.^{2,7} This is thought to be due to activation of the extrinsic coagulation pathway on one hand, and alteration in tissue factor pathway inhibitor on the other.^{35,36} In addition to sepsis, limited mobility,

nephrotic syndrome, and previous DVT were more prevalent in patients who developed DVT. This is in agreement with the findings of the MEDENOX study³³ conducted in 1102 acutely ill immobilized medical patients and found a history of VTE to be one of the independent factors associated with VTE. Furthermore, prolonged bed rest and previous DVT were identified by many studies to be important risk factors for VTE in medical patients.^{2,3,6,33,34,37}

In this study Doppler/US was used for the initial screening and later follow up of patients in the ICU. It is nowadays used routinely for clinical assessment of possible lower limb DVT, with sensitivity and specificity in the femoral and popliteal veins reaching 95%.^{12,38} However, it has less sensitivity in asymptomatic patients and in the ICU possibly due to the presence of lower extremity edema, open wounds, and tenderness.³⁹ This may represent a limitation of our study, as some cases of DVT could have been missed by Doppler U/S. Another limitation is the small sample size of DVT patients, which could have affected the significance of conditions observed to be more common in this group than others.

To conclude, our study is in favor of using UFH twice a day for VTE prophylaxis in medical patients admitted to the ICU as we found the incidence of VTE using this regimen to be comparable to the international incidence reported with the use of either UFH 3 times daily or LMWH. We think the strict adherence to the clinical practice guidelines could have contributed to this low incidence rate. However, our findings need to be confirmed in further studies with larger numbers of ICU patients, especially those with sepsis, limited mobility, or history of previous DVT possibly leading to a more selective VTE screening approach and prophylaxis protocol.

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