Original Article

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Venous Thromboembolism Prophylaxis in Obese Medical Patients: A Retrospective Cohort Study

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Background: Obese patients are 2-3 times more likely to develop venous thromboembolism (VTE), and over 60% of VTE occurs in hospital. Our primary objective was to identify the incidence of objectively documented symptomatic VTE during hospitalization or up to ninety days post discharge. Our secondary objectives were to describe the prescribing patterns of VTE prophylaxis received in hospitalized obese medical patients (body mass index [BMI] ≥30 kg/m^2) as well as risk factors for VTE in obese patients.

Method: A retrospective design was used look at obese patients admitted to a general medicine service at three tertiary care academic teaching hospitals in Calgary, AB, Canada from January 1, 2012 to December 31, 2012. VTE was identified based on clinical diagnosis and incidence was calculated.

Results: There were 443 patients included in the analysis. The average age and BMI were 58.5 years and 41 kg/m^2 respectively, and 70.2% were males. The median length of stay in hospital was 7 days (IQR 4-13). A total of 122 patients (27.5%) of patients did not receive thromboprophylaxis during their hospitalization. Unfractionated heparin (UFH) was the most common agent prescribed (37.9%), and only seven patients received high-dose thromboprophylaxis. The median duration of prophylaxis was 6.5 days (IQR 4-12). Seven patients (1.6%) developed VTE (5 pulmonary embolism and 2 DVT) during the study period, and six of these patients received thromboprophylaxis. In terms of risk for VTE, the median Padua Prediction Score for the study group was 2 (IQR 1-3).

Conclusion: There is very little literature on VTE prophylaxis and incidence of VTE in the obese medical patient. Given the low risk for and incidence of VTE in this study, particularly in the context of 27.5% of the study population not receiving thromboprophylaxis, there is a need for further research to evaluate the efficacy and safety of high dose thromboprophylaxis in the obese medical patient.

Keywords: Venous thrombosis, Thromboprophylaxis, Medical patient, Obesity

Introduction

Between 1985 and 2011, the prevalence of obesity defined as a body mass index (BMI) of 30 kg/m^2 or higher, has increased from 6.1% to 18.3% in Canada. By 2019, it is estimated that over 55% of the Canadian adult population will be overweight (BMI 25-29.9 kg/m^2) (34%) or obese (21%)(1). Obesity is a well-known risk factor for a number of chronic conditions including type 2 diabetes mellitus, venous thromboembolism (VTE) and cardiovascular disease(2). VTE, which includes deep venous thrombosis (DVT) and pulmonary embolus (PE), is a preventable disease associated with considerable morbidity and mortality (3).

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Approximately 60% of all VTE in the population originates in hospitals, either during hospitalization or in the 6-week period post-discharge (3). DVT occurs in 10-26% of general medicine patients who do not receive prophylaxis, however, obese patients are 2 to 3 times more likely to develop VTE due to enhanced platelet activity, a procoagulant state, impaired fibrinolysis and activation of endothelial cells relative to non-obese patients (4-6). The incidence of VTE may increase further if multiple risk factors for thrombosis are present (4).

Medical patients have a significantly heterogeneous risk for VTE. Several risk assessment models (RAMs) have been proposed to evaluate the risk of VTE in hospitalized medical patients. Limitations of most RAMs include lack of prospective validation, applicability only to high risk subgroups, inadequate follow-up time and excessive complexity. The American College of Chest Physicians state the Padua Prediction Score as the best available tool to predict the risk of VTE in medical patients (7).

Pharmacologic thromboprophylaxis is recommended for hospitalized medical patients at high risk for VTE in those who are not bleeding or at a high risk for bleed (7). There is little guidance, however, on the optimal dosing of VTE prophylaxis in obese medical patients as this population was under-represented in landmark clinical trials (8-10). The most recent guidelines from the American College of Chest Physicians do not provide any dosing recommendations on VTE prophylaxis in the obese medical patient. Some authors have suggested increasing the prophylactic doses of low molecular weight heparins (LMWH) by 30% in morbidly obese patients (BMI $\geq$ 40 kg/m^2) (11).

The purpose of the study was to describe prescribing patterns of DVT prophylaxis in a cohort of obese medical patients at three tertiary care centers and to determine the incidence of VTE up to 90 days post discharge.

Study Design

A retrospective chart review was completed to measure the study objectives. Data was obtained from patients with a weight greater than 100 kg admitted to one of three acute care adult hospitals in Calgary, Alberta, Canada (Foothills Medical Centre, Peter Lougheed Centre, and Rockyview General Hospital) from January 1, 2012 to December 31, 2012. The computerized order entry system, Sunrise Clinical Manager (SCM), was used to obtain all data for the study. SCM provides detailed clinical information regarding the hospital stay for all patients admitted to Calgary Zone hospitals, including demographic information, diagnoses, procedures and treatments received, progress notes, laboratory values, and whether the patient died during hospitalization.

Inclusion Criteria

Patients who were ≥18 years of age with a BMI ≥30 kg/m^2 admitted to the internal medicine medical teaching team (MTU) or hospitalist service at the three centres described above were eligible for inclusion in the study.

Exclusion criteria

Patients admitted for less than three days, receiving treatment doses of anticoagulation (including warfarin adjusted to therapeutic INR, unfractionated heparin adjusted to therapeutic activated partial thromboplastin time (aPTT), tinzaparin 175 units/kg daily, dalteparin 200 units/kg daily, enoxaparin 1 mg/kg twice daily or 1.5 mg/kg daily, rivaroxaban 15-20 mg daily, apixaban 2.5-5 mg twice daily, or dabigatran 110-150 twice daily), diagnosis of the admitting patients was VTE, and pregnant women.

Outcomes

The primary outcome of the study was to determine the incidence of objectively documented symptomatic VTE during hospitalization or up to ninety days post discharge was defined as VTE confirmed by ultrasound venous doppler of upper or lower extremities, ventilation perfusion lung scan, computed tomography (CT) scan, venography, or at autopsy.

The secondary outcome was to measure the dosing and duration of pharmacological VTE prophylaxis in obese medical patients. We defined standard dosing of pharmacological prophylaxis as dalteparin 2500-5000 units SC daily, enoxaparin 20-40 mg SC daily, tinzaparin 50-75 units SC daily, unfractionated heparin (UFH) 5000 units SC two to three times daily, fondaparinux 2.5 mg SC daily, rivaroxaban 10 mg daily or apixaban 2.5 mg twice daily.

Obesity adjusted pharmacological prophylaxis was defined as UFH 7500 units SC two or three times daily, enoxaparin 40 mg SC twice daily, dalteparin 7500 units SC daily. Prophylactic doses of fondaparinux, rivaroxaban or apixaban are not been evaluated in the obese patient. If a patient had more than one order for thromboprophylaxis, the last order superseded any previous order.

We examined the baseline risk for VTE by calculating the Padua prediction score for each patient included in the study (appendix 1).12 The Padua prediction score is a validated scoring method for assessing risk for VTE in hospitalized medical inpatients. Individuals with a score

of ≥4 are considered high risk for VTE, whereas those with a score of <4 are considered to be at low risk for VTE. Of note, obesity is assigned a score of one in this risk assessment model; therefore all of our study participants had a minimum score of one. Padua prediction score thromboprophylaxis deemed appropriate if started within 48 hours of admission and continued for 80% of hospital stay (12).

We evaluated the incidence of major bleeding during and two days after prophylaxis was complete. Major bleeding was defined as fatal bleeding, bleeding in a critical area or organ including intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome or overt bleeding associated with a drop in hemoglobin concentration of ≥ 20 g/L or leading to transfusion of two or more units of packed red blood cells (13).

We also examined death within 90 days post-hospital discharge, minor bleeding and incidence of heparin induced thrombocytopenia (HIT) defined as platelet count decrease of 30-50% from baseline within 14 days of initiation of pharmacological prophylaxis, positive HIT assay (latex enhanced immunoassay confirmed by serotonin release assay) (14). In the event of death the diagnosis of PE was accepted if it was confirmed at autopsy or anteceded in the immediate period before death by confirmed non-fatal-PE or DVT. Minor bleeding was defined as clinically relevant overt bleeding not meeting the criteria for major bleeding.

Data Collection

We collected age at hospital admission, sex, height, and weight at the time prophylaxis initiated or most current weight documented. In addition, we collected serum creatinine, thereby calculating creatinine clearance (according to the Cockcroft-Gault formula using adjusted body weight) when thromboprophyalxis was initiated and creatinine clearance was stratified in stages ≥90 mL/min, 60-89 mL/min, 30-59 mL/min, 15-29 mL/min, <15 mL/min (dialysis)(15). Baseline platelet count, admitting service (hospitalist or MTU), primary admission diagnosis (as documented on the discharge summary), comorbidities, length of stay, pharmacological thromboprophylaxis agent used including dose and duration, and receipt of mechanical prophylaxis (sequential compression device or graduated compression stockings) and duration of mechanical prophylaxis were documented. For patients with multiple admissions during the study period, only the first admission was included to avoid repeated measures.

We collected other potential risk factors for VTE including use of erythropoietin stimulating agents, venous compression, inflammatory bowel disease, nephrotic syndrome, central venous catheterization, and paroxysmal nocturnal hemaglobinuria.

Ethics Approval

The study was approved by the University of Calgary Conjont Health Research Ethics Board.

Statistical Analyses

Descriptive statistics were used to describe the study population. Continuous variables that were normally distributed were described using mean and standard deviation, whereas continuous variables that were not normally distributed were described using median and interquartile range. Categorical variables were described using proportions. Receipt of thromboprophylaxis was categorically described, as were secondary objectives of development of VTE, Padua prediction score (categorized between low risk and high risk for VTE), major or minor bleed and death.

Results

There were 777 patients with a BMI ≥30 kg/m^2 admitted between January 1 to December 31, 2012. We excluded 334 individuals: 176 patients received treatment doses of anticoagulation, 37 patients were admitted for less than 3 days, 17 patients had a BMI <30 kg/m^2, 14 were surgical patients, and 8 patients were admitted under an alternative service. An additional 82 admissions were repeat admissions with no VTE documented up to 90 days post discharge, leaving a total of 443 patients included in the study.

Amongst the 443 patients included, 70.2% were male and the mean age was 58.5 years (SD ±17.7). A total of 74.0% of patients (n=328) were admitted to the hospitalist service with equal distribution among the three sites (*Table-1*). Hypertension (51.9%), diabetes (39.4%) and chronic obstructive pulmonary disease (COPD)/ asthma (25.2%) were the most common comorbidities, and infection was the reason for admission in 53.9% of patients.

A total of 313 (70.7%) of patients who received pharmacological prophylaxis, and 8 patients (1.8%) received sequential compression devices. Among those who received pharmacological prophylaxis, UFH was the most common agent prescribed (53.7%), and only 7 patients received dosage adjustments for obesity (*Table-2*).

Table-1: Baseline Characteristics of Patients (n:443)

Characteristic	Data Values
Age (years)	58.5 ± 14.7
Male (%)	70.2
Height (cm)	172.8 ± 22.7
Weight (kg)	121.1 ± 22.7
BMI (kg/m^2)	40.8 ± 9.2
Serum Creatinine (umol/L)	84 (69-114)
Creatinine Clearance (mL/min)	87 (59-116)
Platelets (x 109/L)	212 (164-273)
Padua Prediction Score	2 (1-3)
Comorbidities (%)	
Hypertension	51.9
Diabetes	39.4
COPD/Asthma	25.2
Dyslipidemia	20
Myocardial infarction	18.7
Rheumatological disease	13.6
Heart failure	11.1
Malignancy	7.6
Renal disease	7.1
Stroke/TIA	4.2
PVD	1.8
Reason for Admission (%)	
Infection [a]	53.9
Gastrointestinal/Liver [b]	19.8
Respiratory [c]	15.6
Cardiac [d]	10.5
Renal	9.6
Pain crisis	8
Toxic syndrome [e]	7.8
Central Nervous System [f]	7.1
Endocrine [g]	4.5

Abreviations: **BMI:** body mass index, TIA: transient ischemic attack, PVD: peripheral vascular disease. **(a)** Most common was pneumonia, urinary tract infection, cellulitis, and bacteremia, **(b)** Most common was gastrointestinal bleeding and pancreatitis, **(c)** Most common was acute exacerbation COPD, **(d)** Most common was hypertension and heart failure, **(e)** Moat common alcohol withdrawal and acute poisoning/overdose, **(f)** Most common was delirium, **(g)** Most common was hyperglycemia.

VTE prophylaxis was started within 24hours in 96% (n=300/313) of patients who received pharmacological prophylaxis. Among those who received prophylaxis, the median duration was 6.5 days (IQR 4-12). The median length of stay in hospital was 7 days (IQR 4-13). A total of 81.1% of people (n=99/122) who did not receive VTE prophylaxis did not have a contraindication, however, 13 (10.7%) of these individuals had a Padua score of ≥4, indicating they were at high risk for VTE. Among those who received prophylaxis, 68 (21.2%) of individuals had a Padua score of ≥4. There were seven patients who developed VTE during the evaluation time frame: five who patients developed PE and two patients developed DVT. VTE occurred during the hospital admission in one patient and within 90 days of discharge in the six other patients. Three patients had a low Padua score (<4) and 4 patients a high predictive score (≥4). Five patients received pharmacologic standard dose prophylaxy (two received heparin 5000 units SC twice daily and three received enoxaparin 40 mg SC daily). One patient did not receive VTE prophylaxis and 1 patient received enoxaparin 30 mg SC twice daily.

Table-2: Summary of DVT Prophylaxis

Prophylactic Agent	Num. of Patients (%)
Heparin 5000 U SC twice/daily	146 (33)
Heparin 5000 U SC three/daily	22 (5)
Enoxaparin 40 mg SC daily	110 (25)
Enoxaparin 40 mg SC twice/daily	4 (0.9)
Enoxaparin 30 mg SC daily	1 (0.2)
Enoxaparin 30 mg SC twice/daily	3 (0.7)
Enoxaparin 20 mg SC daily	2 (0.5)
Dalteparin 5000 units SC daily	23 (5)
Fondaparinux 2.5 mg SC daily	2 (0.5)
Sequential compression device	8 (2)
No prophylaxis	122 (28)

There were 21 deaths during the study period. The cause of death was unknown in six cases, and the other 15 deaths were not directly attributed to thrombosis. No major bleeding or heparin induced thrombocytopenia occurred during the study period. There were three minor bleeds reported (1 patient received heparin 5000 units SC twice daily and 2 patients did not receive pharmacological prophylaxis).

Discussion

In our cohort of 443 obese medical patients, 313 patients were receiving pharmacologic prophylaxis (70.7%), 7 of which received obesity-adjusted dosing. Of 7 total patients who developed VTE, 5 were receiving standard dose pharmacologic prophylaxis. Review of patient risk factors for VTE in our study population using the Padua Prediction Score revealed a low risk population.

The Padua Prediction Score was developed in 1180 hospitalized medical patients in Italy; 711 low risk and 469 high risk patients.12 Obesity was defined as BMI greater than or equal to 30 kg/m^2. There were 45/711 (6.3%) obese patients in the low risk group, 19/186 (10.2%) high risk group who received prophylaxis and 12/282 (4.2%) who were high risk for VTE and did not receive thromboprophylaxis. VTE occurred in 2/711 (0.3%) low risk, and 35/469 (7.5%) high risk patients, of which 31/283 (11%) did not receive thrombopro phylaxis and 4/186 (2.2%) who received thromboprophylaxis.

The rate of VTE in the study was higher than that reported in the Padua study in the low risk population and in the high risk group who received standard dose thromboprophylaxis. Patients at extremes of body weight are rarely reported in clinical trials involving anticoagulants. A subgroup analysis of the MEDENOX (enoxaparin) DVT prophylaxis study in medical patients (N: 1102) defined obesity as BMI ≥30 kg/m^2 in males and ≥ 28.6 kg/m^2 in females. There were 200 obese patients. The reduction in the rate of VTE in patients with obesity was 51% in those who received enoxaparin 40 mg SC daily versus placebo (Relative Risk [RR] 0.49, 95% Confidence Interval [CI] 0.18-1.36) (16). In addition, 1118 obese patients were included in a subgroup analysis of the PREVENT (dalteparin) DVT prophylaxis study in medical patients (N=3706) which defined obesity as BMI ≥30 kg/m^2 in males and ≥28.6 kg/m^2 in females (17). The primary end point (a composite of symptomatic VTE, fatal PE, sudden death or asymptomatic proximal VTE) occurred in 2.8% (dalteparin) versus 4.3% (placebo) groups (RR 0.64, 95%CI 0.32-1.28). Analysis suggested dalteparin 5000 units SC daily was effective in reducing VTE in patients up to BMI <40 kg/m^2 but, was not effective in reducing VTE in patients with BMI ≥40 kg/m^2. Another landmark trial with fondaparinux 2.5 mg SC daily versus placebo for DVT prophylaxis in medical patients (n: 839) did not conduct a subgroup analysis of outcomes in obese patients. The mean BMI was 26 kg/m^2 (10).

Wang et al have published the largest study (n: 9241) to date on the efficacy and safety of high dose thromboprophylaxis in the obese patient (18). The study was a retrospective cohort study using data from three hospitals in the United States over a 25 month period. Patients were surgical and medical patients, and were categorized into two groups: BMI less than 40 kg/m^2 (n: 5313) and greater than or equal to 40 kg/m^2 (n:3928). Standard dosing of thromboprophylaxis was UFH 5000 units 2-3 times daily or enoxaparin 40 mg daily. High dose thromboprophylaxis was heparin 7500 units SC 3 times daily or enoxaparin 40 mg SC twice daily. The primary outcome was the identification of hospital-acquired VTE. The average age was 56 years. The median length of stay in patients who developed VTE was 13.4 days versus 4.3 days (P<0.001). High dose thromboprophylaxis was associated with less VTE (Odds Ratio [OR] 0.52, 95%CI 0.27-1, Number Needed to Treat [NNT]=140). No benefit of high dose thromboprophylaxis was found in patients with BMI less than 40 kg/m^2 (OR 1.23, 95% CI 0.72-2.10). VTE was more likely in male patients, those with cancer or history of recent surgery. There was no statistically significant difference in bleeding between standard and high dose thromboprophylaxis. There are limitations to the study, however. The study was retrospective and relied on ICD-9 codes to identify VTE and bleeding events. Unfortunately there was no breakdown of VTE and bleeding between the medical and surgical patients.

In our study, four of the seven patients who developed VTE had a BMI >40 kg/m^2 (average of 51.6 kg/m^2). Three patients received standard dose prophylaxis and developed PE. One patient prescribed enoxaparin 30 mg SC twice daily developed a right basilic/axillary vein thrombosis possibly related to a peripherally inserted central catheter in his right arm. Data from the Wang study suggests thrombosis may have been prevented in these patients if they received high dose DVT prophylaxis with enoxaparin 40 mg SC twice daily or UFH 7500 units SC 3 times daily. The four patients in our population who received enoxaparin 40 mg SC twice daily did not develop VTE.

The main limitations of our study were retrospective design, small sample size and number of thrombotic events reported (1.6%). However, when compared to other recent studies of VTE prophylaxis in general medicine patients our study showed a higher incidence of VTE. Flanders et al conducted a large retrospective cohort in 20,794 general medicine patient (19). The average Caprini Score was 6 (score ≥5 have 40-80% incidence of DVT) (20). Data was collected for VTE prophylaxis during admission, VTE risk factors and VTE events up to 90 days post hospital admission. A total of 226 VTE events (1.1%) occurred during 1,765,449 days of patient follow up. Only 34/226 events (15%) occurred during the index hospital admission. A total of 166 patients (73.5%) who experienced pharmacological prophylaxis during admission. Age greater than 65 years, length of stay greater than 5 days, cancer and central venous catheter were associated with increased risk of VTE. Lederle et al conducted a systematic review of randomized clinical trials of DVT prophylaxis in medical patients comparing unfractionated heparin (UFH) versus no heparin (10 trials; 20 717 participants) and low molecular weight heparin (LMWH) versus UFH (9 trials; 11650 participants)(21). Symptomatic DVT was reported in 0.79% in UFH arm and 0.96% in the control arm and PE in 0.84% in the UFH arm versus 1.2% in the control group. In trials comparing UFH versus LMWH symptomatic DVT was reported in 0.16% in both treatment arms and PE 0.52% in the LMWH arm and

0.74% in the UFH treatment arm. There was no subgroup analysis of VTE or bleeding in obese medical patients in either study. In the study presented 6 of the 7 thrombotic events occurred while patient received DVT prophylaxis.

Due to the small sample size our study can be considered hypothesis generating as our findings suggest that standard dose pharmacological VTE prophylaxis may not be sufficient in the obese medical patient. Our study provided very detailed information on DVT prophylaxis but, with the small number of events reported we were not able to determine if patient factors such as reason for admission or presence of comorbidities increased the risk of VTE.

Conclusion

To our knowledge, this is the first study in obese medical patients looking at VTE risk factors, dosing of DVT prophylaxis and incidence of VTE up to 90 days post discharge. Only 7/443 patients (1.6%) received high dose DVT prophylaxis. The evidence available suggests high dose prophylaxis with UFH 7500 units SC 3 times daily or enoxaparin 40 mg SC twice daily may be most efficacious in patients with BMI $\geq$40 kg/m^2 without an increased risk of bleeding. There is a need for randomized controlled trials of high dose DVT prophylaxis in acute ill obese medical patients to further evaluate the efficacy and safety.

Conflict of Interest

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Appendix-1. Padua Prediction Score to Assess Risk Factors for VTE in Hospitalized Medical Patients [12]

Risk Factor	Score
Active cancer [a]	3
Previous VTE (with the exclusion of superficial vein thrombosis)	3
Reduced mobility [b]	3
Already known thrombophilia condition [c]	3
Recent (≤1 month) trauma and/or surgery	2
Elderly (age ≥70 years)	1
Heart and/or respiratory failure	1
Acute myocardial infarction or ischemic stroke	1
Acute infection and/or rheumatological disorder	1
Obesity (BMI ≥30)	1
Ongoing hormonal therapy [d]	1

a) Patients with local or distant metastases and/or in whom chemotherapy or radiotherapy had been preformed in the previous 6 months
b) Anticipated bedrest with bathroom privileges (either due to patient's limitations or on physician's order) for at least 3 days
c) Carriage of defects of antithrombin, protein C or S, factor V leiden, G20210A prothrombin mutation or antiphosphoplipid syndrome
d) Defined as estrogen containing oral contraceptives or hormone replacement therapy, or selective estrogen receptor modulators

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