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Efficacy and safety of high-dose thromboprophylaxis in morbidly obese inpatients

Tzu-Fei Wang^{1,2}, Paul E. Milligan³, Catherine A. Wong³, Eli N. Deal⁴, Mark. S. Thoenke², and Brian F. Gage²

¹Division of Hematology, Department of Medicine, The Ohio State University

²Department of Medicine, Washington University School of Medicine, Saint Louis, MO

³Center for Clinical Excellence, BJC HealthCare, Saint Louis, MO

⁴Department of Pharmacy, Barnes-Jewish Hospital, Saint Louis, MO

Summary

Background—Obesity increases the risk for venous thromboembolism (VTE), but whether high-dose thromboprophylaxis is safe and effective in morbidly obese inpatients is unknown.

Objective—To quantify the efficacy and safety of high-dose thromboprophylaxis with heparin or enoxaparin in inpatients with weight > 100 kilograms (kg) within the BJC HealthCare system.

Patients/Methods—In a retrospective cohort study, we analyzed 9241 inpatients with weight > 100 kg discharged from three hospitals in the BJC HealthCare system from 2010 through 2012. We compared the incidence of VTE in patients who received high-dose thromboprophylaxis (heparin 7500 units three times daily or enoxaparin 40 milligrams (mg) twice daily) to those who received standard doses (heparin 5000 units two or three times daily or enoxaparin 40 mg once daily). The primary efficacy outcome was hospital-acquired VTE identified by International Classification of Diseases (ICD)-9 diagnosis codes. The primary safety outcome was bleeding events identified by ICD-9 codes.

Results—Among the 3928 morbidly obese inpatients (weight >100kg and body mass index (BMI) 40 kg/m²), high-dose thromboprophylaxis approximately halved the odds of symptomatic VTE (odds ratio (OR) 0.52, 95% CI 0.27-1.00; p-value (p) = 0.050). The rate of VTE was 1.48% (35/2369) in these morbidly obese inpatients who received standard doses of thromboprophylaxis, compared to 0.77% (12/1559) in those who received high doses. High-dose thromboprophylaxis did not increase bleeding (OR 0.84, 95% CI 0.66-1.07, p = 0.15). Independent predictors of VTE include surgery, male, cancer, and BMI.

Conclusions—High-dose thromboprophylaxis nearly halves the rate of VTE in morbidly obese inpatients.

Corresponding author: Brian F. Gage, M.D., 660 South Euclid Ave, Campus Box 8005, Department of Medicine, Washington University School of Medicine, Saint Louis MO 63110, USA, Phone: 314-454-8697, Fax: 314-454-5554, bgage@dom.wustl.edu.

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Keywords

Obesity; obese inpatient; thromboprophylaxis; venous thromboembolism

Introduction

Venous thromboembolism (VTE) is a common problem that can be rapidly fatal, particularly in obese patients with poor cardiopulmonary reserve. Recent studies found that obesity is an increasingly important risk factor for VTE (1, 2), and the obesity epidemic is fueling an epidemic of VTE (3-6). Obese patients are 2 to 3 times more likely to have a VTE (5, 7, 8), twice as likely to suffer from a delayed diagnosis of VTE (9) or develop post-thrombotic syndrome (10). Half of inpatients who die of a post-operative pulmonary embolism (PE) are morbidly obese (11), and morbid obesity increases the risk of fatal PE twelve-fold (12). In summary, VTE prevention is paramount to the care of this population.

For inpatients, anticoagulant prophylaxis is the major mode of VTE prevention, especially because pneumatic compression devices have limited effectiveness in morbidly obese inpatients (13). When clinicians prescribe unfractionated or low-molecular-weight heparin (LMWH) for VTE *treatment*, they adjust doses based on weight (14, 15). In contrast, when prescribing thromboprophylaxis, clinicians typically prescribe fixed doses (e.g., unfractionated heparin 5000 units 2 to 3 times a day or enoxaparin 40 milligrams (mg) once daily), despite evidence that there is a dose-response relationship for thromboprophylaxis (16).

Pharmacokinetic and epidemiologic studies suggest that the standard fixed doses of thromboprophylaxis are suboptimal in obese patients (17-19). When obese patients are given enoxaparin 40 mg, there is a negative correlation between body weight and anti-factor Xa (anti-Xa) levels (18). In contrast, prescribing approximately 0.5 mg/kg of enoxaparin daily (e.g., 80 mg daily in a patient weighing 160 kg) results in anti-Xa levels that are within or near target levels (20). Therefore, Freeman et al. recommended either a fixed high-dose (i.e., enoxaparin 40 mg twice daily) (21) or a weight-based dosing regimen (e.g., enoxaparin 0.5 mg/kg/day) (22) as thromboprophylaxis for obese patients. On the other hand, Nutescu et al. suggested increasing the dose of LMWH by 30% in patients with body mass index (BMI) 40 kg/m^2 (17). Clarity regarding the optimal doses for obese inpatients is needed, given the ubiquitous use of prophylactic heparin and enoxaparin in obese inpatients and their high risk of VTE (23, 24).

Based on these pharmacokinetic and epidemiologic studies, the BJC HealthCare system evaluated increased doses of thromboprophylaxis in inpatients who met two criteria: (1) weight $> 100 \text{ kg}$ and (2) BMI $\geq 40 \text{ kg/m}^2$. Specifically, BJC modified the standard order sets to recommend unfractionated heparin 7500 units three times a day (instead of standard dosing of 5000 units two to three times a day) or enoxaparin 40 mg twice a day (instead of 40 mg once a day) in such inpatients. These recommended orders were phased in between 2007 and 2012. Here, we quantify the effects of the new orders on VTE incidence in three hospitals in the BJC HealthCare system.

Methods

We conducted a retrospective cohort study of hospital-acquired VTE by using data from three hospitals within BJC HealthCare, a large nonprofit health care organization serving the greater St. Louis, mid-Missouri, and southern Illinois regions. The three participating hospitals included one academic teaching hospital, Barnes-Jewish Hospital (BJH), and two community hospitals, Missouri Baptist Medical Center (MBMC) and Barnes-Jewish West County Hospital (BJWC). Our study population consisted of inpatients discharged from January 1, 2010 through February 29, 2012 with a weight > 100 kg and a medication order for thromboprophylaxis with either unfractionated heparin or enoxaparin within the first 48 hours of admission. We limited our population to inpatients with lengths of stay of at least 48 hours.

We utilized electronic height and weight data. Patients with missing height or weight were excluded. To limit extreme heights and weights, we performed a 95% Winsorization, setting the lower and upper 2.5% of height and weight values to the 5th and 95th percentiles. If a patient had more than one thromboprophylaxis ordered within the first 48 hours, the last order within that period superseded any initial order. For example, orders for thromboprophylaxis that were written in the emergency department were superseded by orders written on admission to the inpatient service. We excluded patients with conflicting thromboprophylaxis orders on the same start date. To account for reduced dosing due to renal impairment, we excluded patients with a creatinine clearance of less than 30 mL/min. We analyzed all inpatients with weight > 100 kg, subcategorizing them into two groups: BMI < 40 kg/m² and BMI ≥ 40 kg/m². We defined high-dose thromboprophylaxis as heparin 7500 units three times daily (total of 22,500 units a day) or enoxaparin 40 mg twice daily (total of 80 mg a day).

We identified in-hospital VTE using a modified version of the Agency for Healthcare Research and Quality's Patient Safety Indicator (PSI) 12, version 4.2. Our modifications included extending PSI 12 to non-surgical population and changing one of the included ICD-9 (International Classification of Diseases, Ninth revision) diagnosis codes, "453.8," to "453.89" (the modification was done due to the addition of the fifth digit to ICD-9 codes after the specification of PSI 12, version 4.2. All sub-categorized five-digit codes under 453.8 except for 453.89 referred to upper extremity thromboses and were excluded from our analysis). Other applied diagnosis codes for VTE were listed in Appendix A.

Consistent with PSI 12, we excluded patients under 18 years of age; patients assigned to major diagnostic category 14 (pregnancy, childbirth, and puerperium); and patients with a VTE diagnosis present on admission. To reduce the number of false positive VTE, we further excluded patients with a medication order for VTE treatment within the first 48 hours of admission, as VTE was likely present on admission for these patients. According to internal validations, our method for VTE identification had a sensitivity and negative predictive value of 100%, specificity of 83%, and a positive predictive value of 74%.

We used ICD-9 codes to identify cancer, surgery, and bleeding events. Specifically, we identified bleeding events by using a comprehensive set of ICD-9 codes (25, 26) and cancer

from the ICD-9 codes recommended by Quan et al. (27). Likewise, we identified surgery using an on-line list of the relevant ICD-9 codes (28).

At BJH, the modified order sets were effective as of April 2007, while at MBMC, they started in January 2008 for heparin and July 2010 for enoxaparin. BJWC started the order sets much later, January 2012 for enoxaparin and March 2012 for heparin. We therefore calculated the rate of physician observance of the recommended order sets of high-dose thromboprophylaxis after its implementation for a subset of patients, which included all inpatients at BJH and all inpatients who received prophylactic heparin at MBMC. Physician observance was defined as prescription of high-dose thromboprophylaxis in patients who met both criteria: (1) weight > 100 kg and (2) BMI $\geq 40\text{kg/m}^2$, as recommended by the modified order set. Based on our internal quality control data, more than 90% of thromboprophylactic doses were given as prescribed.

We used the independent sample t-test to compare continuous variables and the chi-square test to compare categorical variables. We used Wilcoxon-Mann-Whitney test to compare median length of stay between VTE and no VTE groups. We used logistic regression to calculate odds ratios (OR). In the logistic model, we considered the interaction of high-dose thromboprophylaxis with either BMI or weight as a continuous variable on the outcome of VTE or hemorrhage. To limit the risk of confounding, we retained variables in the logistic regression that were statistically significant or that had a trend (two-sided p-value < 0.2) that was consistent with prior literature, including age, male gender, race, BMI, weight-based prophylaxis, interaction between BMI and weight-based prophylaxis (BMI x weight-based prophylaxis), cancer, and surgical patients. All analyses were performed using SAS version 9.3.

This study was approved and conducted according to guidelines established by the Institutional Review Boards of Washington University (for BJH and BJWC) and MBMC. The requirement for informed consent was waived because measurements and care performed in the study were part of routine clinical care and confidentiality was maintained.

Results

Patient characteristics

There were 9241 patients with weight > 100 kg who met the inclusion criteria and were discharged from one of the three hospitals in the BJC HealthCare system (BJH, MBMC, and BJWC) between January 1, 2010 and February 29, 2012. Their median height was 175 centimeters and median weight was 115.7 kg.

Age, gender, race, and length of stay differed in the 132 patients (1.4%) who developed VTE compared to those who did not (Table 1). Patients who developed VTE were older (mean age 57.1 vs 54.3 years, $p = 0.02$), were more likely male (74% vs 57.5%, $p < 0.001$) and Caucasian (86% vs 74%, $p = 0.002$). The median length of stay was longer in patients who developed a VTE (13.4 vs 4.3 days, $p < 0.001$). Mean weight and mean BMI were comparable between those who did and did not develop VTE.

Unadjusted analysis of VTE rates

6780 patients were on standard thromboprophylaxis, of whom 103 (1.52%) developed VTE; 2461 patients received high-dose thromboprophylaxis, of whom 29 (1.18%) developed VTE ($p = 0.22$).

Analysis of VTE, stratified by BMI

Of the 3928 morbidly obese patients ($\text{BMI} \geq 40 \text{ kg/m}^2$), most (60%, $n=2369$) received standard thromboprophylaxis. Of these, 35/2369 (1.48%) developed VTE. Of the morbidly obese patients who received high-dose thromboprophylaxis, 12/1559 (0.77%) developed VTE (OR 0.52, 95% CI (confidence interval) 0.27-1.00, $p = 0.050$, Table 2). Among the 5313 patients with $\text{BMI} < 40 \text{ kg/m}^2$, no benefit of high-dose thromboprophylaxis was found (OR 1.23, 95% CI 0.72-2.10, $p = 0.46$) [Table 2].

Independent Predictors of VTE

Logistic regression identified several independent predictors of VTE. The ORs (95% CI) for VTE were 2.2 (1.4-3.5) for male sex, 2.1 (1.4-3.1) for cancer, 4.0 (2.7-6.1) for recent surgery, and 1.04 (1.01-1.08) for each 1-unit increase in BMI (kg/m^2). The interaction between high-dose prophylaxis and BMI (BMI x weight-based prophylaxis) was significant ($p=0.047$), indicating high-dose prophylaxis was more effective in patients with higher BMI.

Analysis of hemorrhage

Of the 2369 morbidly obese inpatients who received standard thromboprophylaxis, 200 (8.44%) developed bleeding. Of the 1559 morbidly obese inpatients receiving high-dose thromboprophylaxis, 112 (7.18%) developed bleeding (OR 0.84, 95% CI 0.66 to 1.07, $p = 0.15$). Similarly, for patients with $\text{BMI} < 40 \text{ kg/m}^2$, there was no association between receiving high-dose thromboprophylaxis and bleeding events (Table 3).

Physician observance

Physician observance per recommended order sets was assessed using a subset of patients (all inpatients at BJH and inpatients at MBMC who received prophylactic heparin). High-dose thromboprophylaxis was prescribed per recommended order sets in 42.1% of patients with both weight $>100 \text{ kg}$ and $\text{BMI} \geq 40 \text{ kg/m}^2$.

Discussion

In our cohort of 3928 morbidly obese inpatients (weight $>100 \text{ kg}$ and $\text{BMI} \geq 40 \text{ kg/m}^2$), high-dose thromboprophylaxis halved the odds of in-hospital VTE (OR 0.52; 95% CI 0.27-1.00, $p = 0.050$). The rate of VTE was 1.48% (35/2369) in morbidly obese patients who received standard thromboprophylaxis and 0.77% (12/1559) in morbidly obese patients who received high-dose thromboprophylaxis, with an absolute risk reduction of 0.71% VTE and a number needed to treat (NNT) to prevent one additional VTE of approximately 140. High-dose thromboprophylaxis did not increase bleeding (OR 0.84, 95% CI 0.66-1.07, $p = 0.15$). Thus, our study demonstrated a feasible and safe intervention to reduce symptomatic VTE in morbidly obese inpatients.

Obesity increases VTE risk via several mechanisms. Obesity induces platelet hyperactivity (2, 29) and increases several procoagulant factors [such as fibrinogen, von Willebrand factors and clotting factors VIII, IX, XI and XII (30-32)], resulting in increased thrombin generation (33). In addition, obesity impairs fibrinolysis via increased levels of plasminogen activator inhibitor-1 and thrombin activatable fibrinolysis inhibitor (32, 34). Obesity also causes activated protein C resistance (34, 35). Finally, adipose tissues release adipocytokines and free fatty acids, which cause inflammation, leukocyte recruitment, platelet aggregation, and endothelial dysfunction (2, 29, 32), thereby leading to thrombosis.

In our study, patients who developed VTE tended to be older and male, and they more often had cancer or a recent surgery. Age is a known risk factor for VTE (36, 37). Prior studies have identified male gender as a risk factor for VTE in special populations, including bariatric surgery (38) and orthopedic surgery patients (39) or patients with a history of VTE (40). In other studies, malignancy has been associated with at least 4-fold risk of VTE (41), with even higher risks from cancers of the brain or pancreas (42). Recent surgery also increases VTE risk (43). The clinical relevance of these risk factors is that high-dose prophylaxis may have the greatest absolute risk reduction in VTE among morbidly obese inpatients who have advanced age, male gender, malignancy, or a recent surgery. The median length of stay was longer in patients who developed VTE compared to those who did not. Because patients were not randomized to length of stay, it is not possible to determine whether the longer hospitalization caused more VTEs or was caused by the VTEs or other confounding conditions.

Our results suggest that the potential benefits of high-dose thromboprophylaxis in bariatric surgery patients apply to morbidly obese inpatients not undergoing bariatric surgery. Borkgren-Okonek and colleagues treated 124 patients (BMI range of 36 to 50 kg/m²) undergoing gastric bypass via Roux-en-y anastomosis with enoxaparin 40 mg twice daily (44). Most (79%) reached a target anti-Xa level, and only one VTE was diagnosed in the study. Singh and colleagues prescribed a similar thromboprophylaxis regimen stratified by BMI and had no VTE in 170 morbidly obese inpatients (45). Among 481 bariatric surgery patients (mean BMI of 50), Scholten et al. found fewer VTE in the 40 mg enoxaparin twice daily cohort (0.6%) than in the 30 mg twice daily cohort (5.4%) [$p < 0.01$], without increased bleeding (46). However, the shorter duration of hospitalization and surgical operation time in the former group might have accounted for the putative benefit (46).

Other studies of high-dose thromboprophylaxis also support our finding that standard doses are suboptimal in morbidly obese patients and high-dose can be safe and effective. For example, Rondina et al. implemented weight-based prophylactic enoxaparin of 0.5 mg/kg daily in 28 hospitalized morbidly obese medical patients (20). No bleeding developed, and most patients achieved anti-Xa levels either within or close to the recommended range. This regimen was more likely to achieve goal anti-Xa levels than were standard doses of either 40 mg per day or 0.4 mg/kg/day (22). Another group evaluated enoxaparin (0.5 mg/kg) in the surgical intensive care unit in 23 patients with BMI ≥ 35 kg/m² or weight ≥ 150 kg and found it effective and safe (47). These studies provided confirmation that high-dose thromboprophylaxis is safe and easy to use. Because enoxaparin is manufactured in pre-

filled (e.g., 40 mg) syringes, a regimen of 0.5 mg/kg may be harder to implement than a fixed high-dose regimen such as 40 mg twice daily.

In our study, although the risk of VTE was halved with high-dose thromboprophylaxis in the target population, the rate of physicians' adoption of this regimen was low. The clinicians' lack of awareness and their fear of iatrogenic bleeding may have contributed to this low utilization. Reassuringly, we found no increased risk of bleeding from prescribing high-dose thromboprophylaxis in the target population. Computerized-alert programs could improve the rate of thromboprophylaxis and prevention of VTEs (48, 49). Thus, they could be utilized to implement the high-dose thromboprophylaxis in morbidly obese inpatients. We are currently implementing such an intervention in all adult hospitals in our health care system.

There are several limitations of this study. First, the p-value was borderline statistically significant ($p = 0.050$). However, we rejected the null hypothesis because this p-value was two-sided, our results were consistent with prior studies, and the interaction between BMI and efficacy of high-dose prophylaxis was highly significant ($p = 0.047$), even after accounting for other known VTE risk factors such as age, gender, cancer, an recent surgery. Second, we relied on ICD-9 codes to identify VTE and bleeding events. This approach might have false positives from patients with VTE present on admission or a superficial thrombosis. By excluding patients with known VTE on admission, patients on therapeutic doses of anticoagulation within the first 48 hours of admission, and patients who stayed less than 48 hours, we reduced these false positives. Third, medication data were based on electronic orders, so administration of prescribed doses could not be assessed. However, our internal data showed high concordance ($>90\%$) of prescription and administration of thromboprophylaxis.

These limitations are offset by several strengths. To our knowledge, this is the largest study quantifying the efficacy of high-dose thromboprophylaxis in the obese population. We included one university hospital and two community hospitals. In addition, we included all medical and surgical inpatients. Therefore, our results are generalizable to most settings. Furthermore, our primary end points are important clinical outcomes: symptomatic VTE and bleeding. Finally, our intervention was easy for clinicians to implement.

In conclusion, we found that high-dose thromboprophylaxis in morbidly obese inpatients approximately halved the risk of in-hospital VTE. Based on this result and related studies in patients undergoing bariatric surgery, we recommend that clinicians use high-dose thromboprophylaxis (e.g. heparin 7500 units three times a day or enoxaparin 40 mg twice a day) in morbidly obese inpatients with weight >100 kg and BMI >40 kg/m² (unless they have renal insufficiency or other contraindication).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Demographics of the cohort, stratified by development of venous thromboembolism (VTE).

	VTE (N=132) Mean (SD)	No VTE (N=9109) Mean (SD)	p Value
Age (years)	57.1 (15.2)	54.3 (13.8)	0.02
Weight (kg) *	119.8 (13.4)	118.6 (13.6)	0.32
BMI (kg/m ²) *	38.7 (5.2)	39.6 (6.5)	0.11
Female gender (%)	25.8 (n=34)	42.5 (n=3870)	<0.001
Non-Caucasian Race (%) **	14.4 (n=19)	26.1 (n=2378)	0.002
Median length of stay (days)	13.4	4.3	<0.001

* Based on 95% Winsorized values

** Non-White Race: includes 2298 African Americans, 8 Asian, 12 American Indian, and 79 Other Race patients.

Abbreviations: kg- kilogram, SD- standard deviation, BMI- body mass index

Table 2
Venous thromboembolic (VTE) events in the cohort stratified by BMI and Prophylaxis.

Population	Prophylaxis	VTE	No VTE	VTE (%)	OR	95% CI	p Value
BMI < 40 kg/m ² (N = 5313)	Standard	68	4343	1.54	ref.		
	High-dose	17	885	1.88	1.23	0.72-2.10	0.46
BMI ≥ 40 kg/m ² (N = 3928)	Standard	35	2334	1.48	ref.		
	High-dose	12	1547	0.77	0.52	0.27-1.00	0.05

Abbreviations: VTE- venous thromboembolism, OR- odds ratio of VTE when high-dose prophylaxis was prescribed, CI- confidence interval, BMI- body mass index, mg- milligrams, u- units, ref.- reference.

High-dose prophylaxis was 80 mg per day if enoxaparin was prescribed and 22,500 units per day if unfractionated heparin was prescribed.

Table 3

Bleeding events in the cohort stratified by BMI and prophylaxis.

Population	Prophylaxis	Bleeding	No Bleeding	Bleeding (%)	OR	95% CI	p Value
BMI < 40 kg/m ² (N = 5313)	Standard	376	4035	8.52	ref.		
	High-dose	62	840	6.87	0.79	0.60-1.05	0.10
BMI ≥ 40 kg/m ² (N = 3928)	Standard	200	2169	8.44	ref.		
	High-dose	112	1447	7.18	0.84	0.66-1.07	0.15

Abbreviations: OR- odds ratio for bleeding when high-dose prophylaxis was prescribed, CI- confidence interval, BMI- body mass index, mg- milligrams, u- units, ref.- reference
High-dose prophylaxis was 80 mg per day if enoxaparin was prescribed and 22,500 units per day if unfractionated heparin was prescribed.