Comparative Effectiveness of Unfractionated and Low-Molecular-Weight Heparin for Prevention of Venous Thromboembolism Following Bariatric Surgery

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Objective: To evaluate the effectiveness and safety of 3 predominant venous thromboembolism (VTE) prophylaxis strategies among patients undergoing bariatric surgery.

Design: Cohort study.

Setting: The Michigan Bariatric Surgery Collaborative, a statewide clinical registry and quality improvement program.

Patients: Twenty-four thousand seven hundred seventy-seven patients undergoing bariatric surgery between 2007 and 2012.

Interventions: Unfractionated heparin preoperatively and postoperatively (UF/UF), UF heparin preoperatively and low-molecular-weight heparin postoperatively (UF/LMW), and LMW heparin preoperatively and postoperatively (LMW/LMW).

Main Outcome Measures: Rates of VTE, hemorrhage, and serious hemorrhage (requiring > 4 U of blood products or reoperation) occurring within 30 days of surgery.

Results: Overall, adjusted rates of VTE were significantly lower for the LMW/LMW (0.25%; P < .001) and UF/LMW (0.29%; P = .03) treatment groups compared with the UF/UF group (0.68%). While UF/LMW (0.22%; P = .006) and LMW/LMW (0.21%; P < .001) were similarly effective in patients at low risk of VTE (predicted risk < 1%), LMW/LMW (1.46%; P = .10) seemed more effective than UF/LMW (2.36%; P = .90) for high-risk (predicted risk ≥ 1%) patients. There were no significant differences in rates of hemorrhage or serious hemorrhage among the treatment strategies.

Conclusion: Low-molecular-weight heparin is more effective than UF heparin for the prevention of postoperative VTE among patients undergoing bariatric surgery and does not increase rates of bleeding.

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Although bariatric surgery has become safer over time, venous thromboembolism (VTE) remains a major cause of potentially preventable morbidity and is the leading cause of death after bariatric surgery. A recent study based on the medical claims for more than 17,000 bariatric surgery patients reports the incidence of VTE as 0.9% in the hospital and 2.2% at 1 month and 3.0% at 6 months postdischarge. The bariatric professional organizations recommend that some form of VTE prophylaxis be used in all patients undergoing bariatric surgery but do not provide specific guidance about specific drugs, dosage regimens, or duration of prophylaxis.

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See Invited Critique at end of article

Most patients undergoing bariatric surgery receive perioperative anticoagulation with either unfractionated (UF) or low-molecular-weight (LMW) heparin. To
our knowledge, only 1 small trial has been performed in the bariatric surgery population and the results of trials in general surgery are conflicting. Unfractionated heparin is much less expensive than LMW heparin. Furthermore, many bariatric surgeons believe that LMW heparin given preoperatively increases the risk of bleeding. The lack of definitive evidence for one treatment over the other in this patient population has led to wide variation in clinical practice.

The goals of this project were to empirically assess the risks and benefits of LMW and UF heparin for patients undergoing bariatric surgery. The study was based on data from the prospective clinical registry of the Michigan Bariatric Surgery Collaborative (MBSC), a statewide consortium involving all hospitals and surgeons performing bariatric surgery in Michigan.

STUDY SETTING

The MBSC is a regional, voluntary consortium of hospitals and surgeons that perform bariatric surgery in Michigan. The goal of the project is to improve the quality of care for patients undergoing bariatric surgery. To do this, the participating hospitals submit data to the MBSC clinical outcomes registry, patient survey, and surgeon survey databases. Three times per year the group meets to examine these data and design and implement changes in care to improve the outcomes of care for bariatric patients. The project is funded by Blue Cross Blue Shield of Michigan/Blue Care Network and coordinated by faculty and staff members from the Center for Healthcare Outcomes and Policy at the University of Michigan.

The MBSC held its first collaborative meeting in June 2005 and enrolled its first patient in June 2006. The MBSC now has the participation of all of its 32 bariatric programs in the State of Michigan, enrolling approximately 6,000 patients per year in its clinical registry. Participating hospitals submit data from a review of the medical records for all of their bariatric surgery patients. This review is conducted for each patient at 30 days after surgery. The information collected includes preoperative clinical characteristics and conditions as well as perioperative clinical care and outcomes. The medical record reviews are performed by centrally trained nurse data abstractors using a standardized and validated instrument. Each participating hospital is site visited annually to verify the accuracy and completeness of their MBSC clinical registry data.

VTE PROPHYLAXIS STRATEGIES

We restricted our analysis to a comparison of 3 dominant VTE prophylaxis strategies used among bariatric surgeons in Michigan. These include preoperative and postoperative UF heparin (UF/UF), preoperative UF heparin and postoperative LMW heparin (UF/LMW), and preoperative and postoperative LMW heparin (LMW/LMW). One of these 3 primary treatment strategies was used for 79% (24,775 of 31,499) of the patients undergoing bariatric surgery during this period. To guard against selection bias (specifically related to outcomes affecting treatment strategy), we measured VTE prophylaxis strategy at the surgery and period level for our primary analysis. To do this, we identified each surgeon’s primary VTE prophylaxis strategy during each quarter of our study period and linked that to the patient-level data. We also repeated our analysis categorizing VTE prophylaxis strategy at the patient level, which resulted in the exclusion of 3,299 patients who did not receive 1 of these 3 strategies, 19 VTE events, and 153 bleeding events. Since the relative differences in the rates of events by treatment group were similar to the primary analysis, they are not presented herein.

Sequential compression devices were used in 98% of the patients in our database and so their usefulness could not be evaluated. Prophylactic inferior vena cava filters were placed in 3.2% of the patients included in this analysis. We have previously reported on the effectiveness of inferior vena cava filters for the prevention of VTE in patients undergoing bariatric surgery,1 and this variable was controlled for in our analysis.

RISK FACTORS

Risk factors for VTE and hemorrhage were empirically derived from our database using multivariate statistical models. Risk factors for VTE included age, body mass index, male sex, current or past smoking, history of VTE, bariatric procedure time more than 3 hours, and procedure type. Risk factors for hemorrhage included age, hypertension, liver disease, and procedure type. A predicted risk for VTE and hemorrhage was calculated for each patient based on these risk factors. For VTE, patients were further divided into low-risk (predicted risk <1%) and high-risk (predicted risk ≥1%) groups.

OUTCOMES

Our primary outcome measures included rates of VTE (a physician diagnosis of a deep vein thrombosis or pulmonary embolism requiring treatment), hemorrhage (bleeding requiring intraoperative or postoperative transfusion or reoperation), and serious hemorrhage (requiring ≥4 U of blood products or reoperation) occurring within 30 days of surgery.

STATISTICAL ANALYSES

The distribution of categorical risk factors for VTE and hemorrhage among the treatment groups was compared using χ² tests. The predicted risks of VTE and bleeding, based on these risk factors, were calculated using logistic regression and compared using 1-way analysis of variance. We used fixed-effects logistic regression to compare outcomes among the treatment groups while controlling for patient risk factors (fixed effects) and clustering at the hospital and surgeon level (random effects). We used fixed-effects logistic regression to compare outcomes within surgeons who switched from one to another treatment strategy during the period of our study. Since the results were similar to the mixed-effects analysis, they are not shown herein. All statistical analyses were performed using STATA version 11.2 (StataCorp).

RESULTS

The distribution of risk factors for VTE (age, body mass index, male sex, current or past smoking, history of VTE, procedure time >3 hours, and procedure type) and hemorrhage (age, treated hypertension, liver disease, and procedure type) across VTE prophylaxis groups is given in Table 1. There were small but statistically significant differences in age, body mass index, male sex, treated hypertension, and liver disease across VTE prophylaxis groups. There were larger differences in procedure time and procedure type. Specifically, the UF/UF group had more laparoscopic adjustable gastric...
In this observational cohort study, we assessed the comparative effectiveness of the predominant VTE prophylaxis strategies in bariatric surgery. We found that LMW heparin is more effective than UF heparin for the prevention of VTE and that it does not increase risks of bleeding in patients undergoing bariatric surgery.

Our results should be evaluated in the context of the results from other studies. A recent meta-analysis reported on the incidence of VTE and bleeding among laparoscopic bariatric surgery patients. Nineteen studies were included with a total of 7590 patients. Unfortunately, this study combined the results for patients receiving “standard prophylactic regimens” of either UF or LMW heparin, reporting a weighted mean incidence of symptomatic pulmonary embolism as 0.5% and major bleeding as 3.6% or 1% depending on the definition used. To our knowledge, only 1 study directly compared UF and LMW heparin. With 238 patients in each group, rates of VTE were 0.4% and 0% and rates of bleeding were 1.3% and 5.9% in the UF and LMW heparin groups, respectively.

In general surgery, the risks and benefits of UF and LMW heparin have been assessed in 8 meta-analyses and systematic reviews. Some studies have shown greater effi-

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**Table 2. Multivariate Comparison of VTE Prophylaxis Groups on Risks of VTE and Hemorrhage**

<table>
<thead>
<tr>
<th>Outcome by Treatment Category</th>
<th>Adjusted Rate</th>
<th>Adjusted OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UF/UF</td>
<td>0.68</td>
<td>[Reference]</td>
<td></td>
</tr>
<tr>
<td>UF/LMW</td>
<td>0.29</td>
<td>0.43 (0.21-0.91)</td>
<td>0.03</td>
</tr>
<tr>
<td>LMW/LMW</td>
<td>0.25</td>
<td>0.34 (0.19-0.62)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Low-risk subgroup</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>(predicted risk of VTE &lt;1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UF/UF</td>
<td>0.59</td>
<td>[Reference]</td>
<td></td>
</tr>
<tr>
<td>UF/LMW</td>
<td>0.22</td>
<td>0.31 (0.13-0.72)</td>
<td>0.06</td>
</tr>
<tr>
<td>LMW/LMW</td>
<td>0.21</td>
<td>0.30 (0.16-0.56)</td>
<td>&lt;.001</td>
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<tr>
<td>High-risk subgroup</td>
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<tr>
<td>(predicted risk of VTE ≥1%)</td>
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<tr>
<td>UF/UF</td>
<td>2.12</td>
<td>[Reference]</td>
<td></td>
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<tr>
<td>UF/LMW</td>
<td>2.36</td>
<td>1.09 (0.27-4.32)</td>
<td>.90</td>
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<tr>
<td>LMW/LMW</td>
<td>1.46</td>
<td>1.11 (0.22-1.11)</td>
<td>.10</td>
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<tr>
<td>Hemorrhage</td>
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<td></td>
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<tr>
<td>UF/UF</td>
<td>1.69</td>
<td>[Reference]</td>
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<tr>
<td>UF/LMW</td>
<td>1.86</td>
<td>1.02 (0.66-1.59)</td>
<td>.93</td>
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<tr>
<td>LMW/LMW</td>
<td>1.65</td>
<td>0.94 (0.63-1.41)</td>
<td>.78</td>
</tr>
<tr>
<td>Serious hemorrhage</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>UF/UF</td>
<td>0.46</td>
<td>[Reference]</td>
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</tr>
<tr>
<td>UF/LMW</td>
<td>0.60</td>
<td>1.05 (0.51-2.15)</td>
<td>0.90</td>
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<tr>
<td>LMW/LMW</td>
<td>0.38</td>
<td>0.75 (0.38-1.47)</td>
<td>0.40</td>
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</tbody>
</table>

**Abbreviations:** LMW/LMW, low-molecular-weight heparin preoperatively and postoperatively; OR, odds ratio; UF/LMW, unfractionated heparin preoperatively and low-molecular-weight heparin postoperatively; UF/UF, unfractionated heparin preoperatively and postoperatively; VTE, venous thromboembolism.
cacy for LMW than for UF heparin\(^6\)\(^7\) while others have shown equivalent efficacy.\(^5\)\(^6\)\(^7\) Some studies have shown equivalent rates of bleeding with LMW and UF heparin\(^4\)\(^6\)\(^8\) while others have shown lower rates of bleeding with LMW\(^11\) or low-dose LMW heparin\(^7\)\(^9\) compared with UF heparin.

While, to our knowledge, our study is by far the largest study in this patient population, there are nonetheless a number of limitations that should be considered in the interpretation of our findings. First, our study is observational and so there is the potential for unmeasured confounders to have influenced the findings. While our clinical registry contains data for the large majority of known risk factors for both VTE and bleeding, some variables known to have a strong effect on these outcomes were not available for this analysis. Specifically, hypercoagulable states (eg, factor V Leiden, activated protein C resistance, and protein C deficiency) and hemophilia are not variables that are included in our registry. However, there is little evidence that patient risk factors affect the choice of VTE prophylaxis strategy, which is largely determined by the standard practice of the treating bariatric surgeon or hospital.

Since the choice of VTE prophylaxis is so strongly associated with the treating bariatric surgeon and hospital, another consideration is whether it is the treatment that is responsible for the outcomes or other related characteristics of the surgeon or hospital. One example of this type of selection bias would be if surgeons with poorer technical skills tend to favor UF heparin because of a belief that LMW heparin will cause bleeding. Because our study took place in the context of a quality improvement collaborative where we had been repeatedly feeding back data to our participants on the risks and benefits of UF and LMW heparin, we were able to evaluate this possibility using a fixed-effects analysis. Specifically, this analysis assesses rates of VTE and bleeding among the surgeons who switched from one strategy to another during the course of our study period. This did not seem to be the case because our results were very similar to the primary mixed-effects analysis.

Another concern for this study is that patient outcomes have a large effect on the choice of treatment given postoperatively. A patient who has intraoperative or early postoperative bleeding may not receive any postoperative prophylaxis. A patient who has a postoperative VTE on the other hand, may receive multiple types of postoperative prophylaxis. Therefore, excluding patients who did not receive 1 of 3 standard strategies would have excluded a lot of patients with the outcomes of interest. For this reason, we assessed the VTE prophylaxis strategy at the surgeon and period level for our primary analysis. However, we repeated our analysis with patient-level measures of VTE prophylaxis to assure that our findings did not depend on the choice of analysis performed. Our results were similar whether the intervention was measured at the surgeon or period or patient level.

Our clinical registry lacks data about the doses of heparin used for VTE prophylaxis. For this reason, we were unable to assess how different dosing affects the relative risks and benefits of UF and LMW heparin in our study population. In addition, our clinical registry captures clinically diagnosed cases of VTE requiring treatment but does not require any kind of confirmatory diagnostic testing. However, any resulting misclassification of outcome would be random and therefore would bias our results toward the null (ie, would underestimate treatment effects).

In summary, this large, observational study provides strong evidence that LMW heparin is more effective and as safe as UF heparin for prevention of VTE among bariatric surgery patients. The bariatric surgery professional societies should act to revise their guidelines to minimize the risks of this potentially devastating complication among bariatric surgery patients.
The data compiled through the MBSC suggest that obese patients. In several studies, LMW heparin has been noted to have greater absorption, which may be particularly important in those patients treated with prophylactic regimens of unfractionated heparin or enoxaparin.

Conflict of Interest Disclosures: None reported.

REFERENCES


Venous Thromboembolism Prophylaxis

One Size Does Not Fit All

For the past 30 years, based on multiple studies involving thousands of general surgery patients, the standard method of preventing VTE complications in surgical patients was to administer UF heparin (5000 U subcutaneously) 2 hours prior to the surgical procedure and continue that dose every 12 hours until the patient was ambulatory.1,2 More recently, however, several high-risk patient groups have been identified in whom this type of prophylaxis is inadequate. These groups include trauma, orthopedics, neurologic, and, based on the article by Birkmeyer et al,3 bariatric surgical patients. The VTE risk may be as high as 3% among patients undergoing bariatric surgery and pulmonary embolism is the number one cause of death in this group. Low-molecular-weight heparin has a greater affinity for antithrombin than UF heparin and a greater bioavailability through easier subcutaneous absorption, which may be particularly important in obese patients. In several studies, LMW heparin has been shown to be more effective in preventing VTE than UF heparin.3,7 The data compiled through the MBSC suggest that patients who received LMW heparin both preoperatively and postoperatively had a 66% lower VTE rate than those who received UF heparin, with an acceptable bleeding risk. In addition to decreasing morbidity and mortality, prevention of VTE may have financial implications for providers, because the Centers for Medicare & Medicaid Services considers deep vein thrombosis a preventable complication.

While a step in the right direction, the study by Birkmeyer et al falls short of providing sufficient data to support a level 1, evidence-based recommendation for bariatric surgeons. The type, dose, and duration of administration of LMW heparin are unknown. This is particularly important since the risk for VTE persists for several months postdischarge. All of the patients in the study were apparently also wearing sequential compression devices but the true value of combination therapy is not addressed. Also, there were a number of patients with prophylactic vena cava filters inserted, a mechanism that may decrease fatal pulmonary embolism but increase deep vein thrombosis formation. Also unknown is how many patients underwent screening for deep vein thrombosis, which would presumably increase the rate of this complication for some surgeons through a surveillance bias. In the future, cost-effective VTE prophylaxis will be guided by considerations of patient weight and point of care coagulation measures to guide dosage because it is apparent that in the use of an anticoagulant, one “size” does not fit all.

M. Margaret Knudson, MD