Full weight-based dosing of lovenox versus a titration protocol in morbidly obese patients admitted with venous thromboembolic disease: a randomized trial.

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A. Introduction

Pulmonary embolism (PE) and deep-vein thrombosis (DVT) are dangerous conditions that are considered part of the same spectrum of diseases collectively referred to as venous thromboembolism (VTE). Unfractionated heparin (UFH) has remained first-line therapy for VTE for decades. Recently, a family of compounds known as low-molecular weight heparins (LMWH) have been developed. Due to decreased protein binding in the serum, LMWH have a longer half-live than UFH, allowing for subcutaneous daily or twice daily administration. While IV infusion rate for UFH requires frequent adjustment based on PTT levels, more predictable pharmacokinetics of LMWH obviates the need for monitoring As a result, it became possible for the first time to complete treatment for VTE in an outpatient setting. In addition, LMWH has a lower risk of heparin-induced thrombocytopenia (1).

Several randomized clinical trials have been performed to evaluate the safety and efficacy of LMWH compared to UFH (2-7). A meta-analysis of these trials (8) demonstrated that only about a thousand patients total in each arm were involved. Therefore, given the low incidence of adverse outcomes heparin is meant to prevent, sufficient power is lacking to conclude definitively that LMWH is equivalent to UFH in efficacy and safety (Table 1). For example, to say with power of 0.8 that a difference of 1% in the incidence of recurrent VTE at a 3-month endpoint would be detected in a trial, about 8,000 patients would need to be enrolled. However, despite the absence of such data, LMWH has been approved by the FDA for a variety of indications, including treatment of VTE (10). According to the most recent guidelines of the American College of Chest Physicians, which traditionally publish guidelines concerning anticoagulation and antiplatelet therapy, LMWH is recommended with equal weight to UFH for treatment of VTE (11).

One patient population where optimal approach to VTE treatment has not been defined yet is the obese patient. Most trials comparing LMWH to UFH did not specifically exclude obese patients but did not have sufficient numbers to analyze this subgroup individually. No outcome data, and therefore no guidelines, for treatment of VTE in obese patients are available (9, 10, 11, 12). Full weight-based dosing raises a theoretical concern for overdose, since lovenox may not be distributed in fat as well as in other tissues (12). While anti-Xa levels can be used to achieve an optimal therapeutic dose of LMWH in an individual patient, this requires time-sensitive phlebotomy (4 hours after the dose). In addition, optimal levels of anti-Xa activity have not been as rigorously defined as APTT levels for UFH therapy. Most trials of LMWH did not measure anti-Xa levels (Table 2).

Full weight-based dosing of a commonly used LMWH, enoxaparin (lovenox) in obese patients was addressed in a recent study (13). Over two hundred patients, including seventy with a BMI >30, received a course of lovenox for a variety of indications at a full weight-based dose. Anti-Xa levels were measured in all subjects. Of the two populations that were at theoretical risk for supratherapeutic anti-Xa levels in the study, i.e. obese patients and patients with renal impairment, only the latter group indeed showed supratherapeutic levels. The authors conclude that "dose adjustment is not required for obese patients." However, outcome data in this study is limited to bleeding rates. In addition, only 20% of patients in this study received lovenox for VTE treatment.

Current options at CPMC for treatment of VTE include UFH or lovenox at a maximum dose corresponding to 120kg followed by dose titration based on anti-Xa levels.

B. Hypothesis

In patients over 120 kilograms admitted to the hospital with confirmed VTE, full weight based dosing will lead to shorter length of stay without significant impact on outcome, as compared to the titration protocol.

C. Outcomes

The primary outcome in this study will be length of stay in hours from triage time to the time of the discharge order. In addition, CT PE protocol and lower extremity venous ultrasound with dopplers will be performed in every patient on admission (day 1), day 7 and day 90, to assess the secondary outcomes of (1) recurrent VTE at 7 days and 90 days; (2) bleeding (3) all-cause mortality at 7 days and 90 days; and (4) the combined end-point of all-cause mortality and VTE at both 7 days and 90 days.

D. Study design

This will be a randomized, open-label study comparing two dosing regimens: a full weight-based dose of lovenox, without anti-Xa level monitoring, vs titration protocol beginning at the dose corresponding to 120 kg and titrating up based on daily anti-Xa levels.

E. Statistical analysis

Unpaired t-test will be used to compare length of stay, while chi-squared test will be used for secondary outcomes. The data will be analyzed on an intention-to-treat analysis.

F. Sample size

To detect a difference of at least 1 day in length of stay with power=0.8 and $p<0.05$, assuming 5 day mean length of stay with SD=1, 17 subjects will be required in each arm. Assuming SD=3, 140 subjects will be needed in each arm. Only large effects in secondary outcomes are expected to be seen. For example, only an increase from 5 to 16% rate of recurrent PE will be detected.

G. Subject selection

Inclusion criteria will be the following: (1) admission diagnosis of DVT/PE (2) admission weight 120kg or higher (3) 18 yo or older (4) able to give informed consent.

Exclusion criteria will be the following: (1) pregnancy, due to different pharmacokinetics of lovenox in pregnant women; (2) participation in another study; (3) INR >2.0, as such patients may not need to receive heparin; (4) contraindication to lovenox and (5) renal impairment (Cr Cl <30), since in such patients anti-Xa level monitoring is mandatory.

H. Risks and benefits

Based on data described above there is currently equipoise regarding the efficacy and safety of the two dosing regimens compared in this study. The full weight-based regimen may may potentially lead to a higher rate of bleeding complications. On the other hand, it may be more effective by reaching the therapeutic dose faster than the titration protocol, potentially shortening length of stay.

I. References

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Table 1. Data from Ref. 8

	LMWH	UFH
Recurrent symptomatic VTE at 3 months	3%	4.5%
Major bleeding	1.4%	2.3%
Minor bleeding	6.8%	5.5%

Table 2. Summary of the data from major trials comparing LMWH to UFH for treatment of VTE with respect to the obese patient population

Trial	Pts	Obesity-based exclusion	Weight, kg	Anti-Xa measured?	Length of stay (LMWH)	Length of stay (UFH)
Thery (1991)	101	no	70-80	Subset only	NR	NR
COLUMBUS (1997)	1021	no	NR	no	6.4+/- 7	9.4+/-8
Simonneau (1997)	612	no	74+/-14	no	NR	NR
Decousus (1998)	400	no	NR	no	NR	NR
Hull (2000)	200	no	NR	yes	NR	NR
Merli	900	no	41-155	no	NR	NR