Review of current evidence available for guiding optimal Enoxaparin prophylactic dosing strategies in obese patients—Actual weight-based vs fixed

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Key Words:

Enoxaparin; dosing strategy; obese; prophylaxis; obesity; Fixed dosing; Capped dosing; Weight-based dosing; actual weight;

Abstract:

Background: The current debate over the optimal Enoxaparin prophylactic dosing strategies in obese patients centre around whether it should be based on the actual weight of the patient (i.e. weight-based), or at an artificially fixed amount, as it is the case in Australia (40mg daily). The vast majority of the evidence available today is laboratory-based, measuring serum Antifactor-X_a activities as a marker for physiological response.

Aim: The aim of the parent study is to compare the clinical outcomes for obese patients who received fixed doses of enoxaparin compared to those who received weight-based doses within the licensed dosage recommendations. This review was conducted to examine whether a gap in knowledge exists in relation to dosing obese patients with enoxaparin as VTE prophylaxis after hospital admission to aid in development of the parent study concept.

Method: Databases such as Medline, EBSCOhost, ProQuest were interrogated using combinations of words such as "enoxaparin", AND "dosing strategy", AND "obese/obesity" AND "prophylaxis". Only eleven out of 14 primary studies which were considered to be sufficiently similar in methodology and anticipated outcomes were reviewed and analysed.

Results: Pooled data from the eleven studies suggested that weight-based or higher-than-fixed dosing had a 36.2% higher success rate than fixed dosing, and was more likely to achieve the desired serum Anti-X_a activity levels (52.2% and 16% respectively). The rate of failure to

achieve this is significantly lower in the weight-based groups (13.3%) than in fixed-dose groups (18.5%). These eleven studies reviewed included 601 patients in total.

Conclusion: There is insufficient evidence to support or negate the current enoxaparin health outcomes in obese and very obese patients due to the lack of post-discharge follow-up from hospitals. Further research is required to compare long-term outcomes after fixed and weight-based dosing of enoxaparin. The optimal dose of enoxaparin per kilogram of body weight for prophylaxis remains to be determined.

1. Introduction:

Enoxaparin is widely used for number of cardiovascular indications. It is a semi-synthetic Low Molecular Weight Heparin (LMWH) of approximately 4500 Daltons in molecular weight. LMWH is an indirect thrombin inhibitor, initiated through forming a complex with anti-thrombin, mediated through the pentasaccharide sequence located along the LMWH chain causing a conformational change to the anti-thrombin. This complex then acts as a catalyst to accelerate the inactivation of coagulation Factor-X_a leading to amplified anti-thrombin actions, by 1000-fold, with thrombin and Factor-X_a. (1, 2). LMWH promotes the release of Tissue Factors Pathway Inhibitor (TFPI) from the vascular endothelium and fibrinolysis. To a lesser extent than unfractionated heparins, LMWHs reduce the level of the von Willebrand factor (vWf), inhibit the pro-coagulation effect of leukocytes and inhibit monocyte adhesion. One of enoxaparin's key indications in a hospital setting is its use as prophylaxis against venous thromboembolism (VTE), which includes both pulmonary embolism (PE) and deep-vein thrombosis (DVT). Its fast onset of action provides protection against VTE events, as well as a superior profile in both efficacy and safety compared to warfarin, make it the 'drug of choice' for many clinicians.

Due to its nature as a LMWH, it is also referred to as 'fractionated heparin'. Since it is cleaved and stabilised ex-vivo during the manufacturing process, before it is administered to the human body, it exhibits a more stable and predictable pharmacokinetic profile (2), resulting in a superior choice to unfractionated heparins for medium- to long-term prophylaxis against VTE. This is particularly important in a community setting or post-discharge from hospital, where less direct medical care and monitoring are available to

patients. Therefore, due to its comparatively fewer incidences of haemorrhagic events and thus a safer choice in prophylactic therapy, it is now a clinicians' choice for prophylaxis against VTE over its unfractionated counterpart (3).

2. Materials and Method:

The literature search was conducted using the Primo Search® search engine to access databases such as Medline, EBSCOhost, ProQuest. The search was conducted using the terms, or combination of those terms, including 'enoxaparin', 'dosing', 'weight', 'obesity' and 'prophylaxis', plus any one or all of the following terms: 'DVT (Deep Vein Thrombosis)', 'PE (Pulmonary Embolism)' or 'venous thromboembolism'.

The following criteria were developed to select the publications included in this review. For a study to be included, it had to be:

- Original research;
- Peer reviewed;
- Published;
- Patient-control design;
- Evidence of structured statistical analysis performed, and weight was one of the study variables.

The research parameters must also include weight at least as part of its consideration, if not one of the primary inclusion criteria. Both retrospective and prospective studies were included in this review.

These papers were then analysed for similarities and differences between study aims, target patient group(s), and methodology. Studies that were deemed to be sufficiently similar were included in this review.

3. Results:

A total of 14 peer-reviewed publications, meta-analyses and guidelines were found to be original publications and relevant to this topic, two studies were excluded as the method and markers were different to that of the other twelve studies (4, 5). The former was excluded on the grounds that they used monitoring techniques and markers that are non-haematological; the latter was targeting a different demographic (paediatric). Twelve publications measured the Anti-Factor X_a (anti-X_a) activity as a clinical endpoint or surrogate marker for the apparent efficacy of enoxaparin in test subjects, with only one publication that took patients' post-discharge monitoring into its primary consideration (6). One study used, in conjunction with anti-X_a levels, Thrombin-Antithrombin concentration levels as a marker (7). It enrolled five patients of which only four agreed to be followed up after discharge from the hospital. This sample is small and constitutes only 8.6% of total patients who received enoxaparin prophylaxis, which means that the findings may not be consistently reproducible and accordingly it was excluded, leaving only eleven studies that can be directly compared.

3.1 Table 1

Constituents and patient demographic

	Cumulative Total of participants included in studies.	**Reported Anti-X_a activity**	**Reported Clinical Outcomes**	**Reported Anti-X_a activity, clinical outcomes and other parameters**
Male	623	591 (94.9%)	32 (5.1%)	(not available)
Female	1289	1121 (87.0%)	168 (13.0%)	(not available)
Unknown	424	0	0	224

Total	2336	1912 (81.8%)	200 (8.6%)	224 (9.6%)

When Anti-X_a activity levels were used as the surrogate marker for enoxaparin prophylaxis (11 studies out of reviewed 14), dosing was either 'fixed' dose at 40mg daily and was considered to be sufficient, or higher dose(s) weight-based dose, usually 0.5mg/kg once daily, or in divided doses twice daily. These two groups included some head-to-head comparison studies, whilst others have taken the null hypothesis of 'Weight-based dosing is necessary for obese patients'. The latter of those tend to select an entire sample of patients who are overweight and give them fixed dosing and to compare them to those given weight-based dosing; whilst the former give both the 'normal' weight and 'obese' patient groups the same fixed dose, and compare the resultant the Anti-X_a activity in each group.

It was also worth noting that each study's target Anti-X_a levels might vary, ranging from <0.1-0.5 IU/ml (8), to 0.18-0.44 being 'therapeutic' according to *Simone et al*. The serum levels in most of these studies were taken as post-dose peak levels, and repeated if multiple doses were administered. It was beyond the scope of this review to consider each single range of those studies individually. Therefore, 'success' was defined as the ability to reach the subjective target of each of these studies' pre-determined range(s).

3.2 Table 2

Pooled data for 11 relevant studies – Ability to achieve relative serum Anti-X_a activity levels for Fixed vs Weight-Based Dosing

Primary author & reference [n(total) = 601]	***n* & (percentage reached target Anti- X_a)**	**Fixed (or lower than Fixed) Dosing successful (%)**	**Fixed (or lower than Fixed) Dosing unsuccessful (%)**	**Weight-based (or higher than Fixed) Dosing successful (%)**	**Weight-based (or higher than Fixed) Dosing unsuccessful (%)**
Kopelman, T. R. (8)	124 (73.4%)	60	30	31	3
Hiscock, R. J. (9)	80 (67.5%)	(not available)	(not available)	54	26
Bickford, A. (10)	86 (86.0%)	(not available)	(not available)	74	12
Freeman, A. (11)	31 (67.7%)	2	9	12	8
Ludwig, K. (12)	23 (100%)	(not available)	(not available)	23	0
dos Reis Macedo, L. G. (13)	28 (85.7%)	3	4	21	0
Rondina, M. (14)	28 (0%)	0	28	n/a	n/a
Simone, E. (15)	51 (70.6%)	20	15	16	0
Rowan, B. (16)	52 (30.8%)	2	17	14	19
Bazinet, A. (17)	81 (85.2%)	(not available)	(not available)	69	12
Frederiksen, S. G. (18)	17 (52.9%)	9	8	n/a	n/a
Total Number &	**601**	**96**	**111**	**314**	**80**

Primary author & reference [n(total) = 601]	*n* & (percentage reached target Anti- X_a)	Fixed (or lower than Fixed) Dosing successful (%)	Fixed (or lower than Fixed) Dosing unsuccessful (%)	Weight-based (or higher than Fixed) Dosing successful (%)	Weight-based (or higher than Fixed) Dosing unsuccessful (%)
Percentage of Total Pooled Data	**(68.2%)**	**16.0%**	**18.5%**	**52.2%**	**13.3%**

Whilst some studies such as *Rowan et al.* (2008) explicitly state the mean BMI of the majority of the surgical patient cohort (e.g. 48.5kg/m^2 in 82% of subjects), others have only included mean weight of its participants receiving trauma-related surgery (103.3kg +/- 20.8kg), with no clear indication of BMI or even height (8). This appears to indicate a major gap in the availability of studies with consistent patient demographics or record of physical attributes.

4. Discussion:

There appears to be insufficient evidence to guide clinical practice surrounding the dose selection of enoxaparin when administered to obese or morbidly-obese adult (19) patients for prophylaxis against venous thromboembolism (both Pulmonary Embolism and Deep Vein Thrombosis). The controversy of enoxaparin prophylaxis dosing largely falls under two groups: those advocating for a fixed dosing (5, 9, 20) and those advocating for a weight-based dosing (8, 10, 14). The former group express an opinion that the dose, regardless of the actual patient weight, should be limited to or capped 40mg daily. The latter believes that there should be no such artificial cap, and patients should be dosed according to their actual weight as per the current treatment requirement. In Australia, The National Health and Medical Research Council (NHMRC) guidelines regarding the use of enoxaparin and other Low Molecular Weight Heparins in prophylactic therapy did not consider this particular subset of patients(21). The official product information of enoxaparin states clearly that this area remains unclear, and the dosing regimen for prophylaxis is a ‘recommended guideline’ only (22).

All 11 studies included in Table 1 used laboratory results of Anti-X_a activity as their primary outcome, or as one of its primary outcomes. The results, from the 11 studies suggest that

there may be a strong relationship between weight and desired Anti-Xa activity levels (52.2%). Whilst compared to the success of fixed dosing (16.0%), it is difficult to draw a robust conclusion based on the finding of the eleven studies as their samples were all relatively small, with many of them showing no clear indication of a power-calculated sample size in the study designs. Additionally, they demonstrate minimal clinical monitoring after hospital discharge as they mostly conclude at the point of discharge from hospitals or high dependency care settings. Consequently, these studies offer probability but no strong evidence to indicate the clinical success for either of these methods of dosing.

A retrospective 6-month follow-up study by *Woo, et al.* (2013) of patients, who had undergone bariatric surgical procedures (as indication for recognised obesity) and immobilisation due to surgery or due to morbid obesity (10). They concluded that 'a 2-week VTE prophylaxis regimen using LMWH (enoxaparin)' was effective (against VTE/PE) and associated with low incidences of (bleeding) complications (6). This study was of significant importance to this review as it has taken into account the clinical outcomes of enoxaparin prophylaxis in an obese population as one of its primary measureable variables. The *Woo, et al.* (2013) study was retrospective and observational in nature, however, it was not randomised or controlled with other patients. As such, the results may not be applicable to other obese and morbidly obese patients who underwent other type surgeries or immobilisation.

Although excluded from this pooled analysis, there is a study that utilised a paediatric sample group (2-18 years of age) and came to the conclusion that the two competing methods of dosing should be comparing between 'Fixed' or 'reduced' to a more conservative dosing – lower than the usual 1mg/kg twice daily regime – rather than the 'fixed' or 'Weight-based' dosing strategies in adult populations (5). Whilst this paediatric study has some merit in guiding practice on the importance of taking body size and weight into account due to its small sample size (n = 59) and a broad spread of ages (2-18 years of age), and the difference in pharmacokinetics and physiological maturity, it is difficult to generalise its finding to other paediatric or adult general population of patients. These patient populations differ greatly in a number of key parameters: weight (36.1-112 kg), height (117-175 cm) and, most importantly, difference in pharmacokinetics, especially enzyme maturity and ability to metabolise drugs. These parameters, in clinical settings, are often detected by their surrogate markers such as liver function tests, renal function tests and blood serum levels.

A recent meta-analysis by *Hanley et al.* (2010) agreed that studies focusing on clinical outcomes in obese patients based on different methods are necessary, not only to validate these metrics of measure, but to ultimately ascertain the best dosing strategy. This is a very important factor in this field of studies, since obese- to morbidly-obese individuals have a higher absolute LBW (though lower by proportion) than their normal-weight counterparts (23). There may be several contributing factors to that, such as larger amounts of vasculature and associated blood flow required to support adipose tissues than non-obese persons, and the additional fluid retained for normal physiological function for these tissues in the form of intracellular fluids. These contributing factors may constitute up to 40% of the obese body weight being lean body tissues, despite the decrease of LBW as proportion of Total Body Weight (TBW) (24). For example, if the uppermost healthy limit of an individual's body weight (with respect to BMI) is 80 kilograms and the actual body weight is 120 kilograms, this translates to an absolute increase of LBW due to obesity by as much as 16 kilograms, or 13.3% of TBW – a clinically significant consideration.

Some experts argue from physico-chemical principles that, enoxaparin compound is a large (4,500 Daltons or larger) and mostly non-polar molecule, and therefore it *should* diffuse into fatty tissues in clinically significant amounts (25). Whilst other experts in the field argue that, given the nature of this formulation of enoxaparin being a *sodium* salt, it is highly unlikely that it is lipid-soluble to a significant extent due to the likely hydrophilicity of compounds containing monovalent ions. Therefore, as physico-chemical properties dictate again, only LBW should be used as the sole 'size descriptor' for dosing. However, this contradicts the use of weight-based dosing principle in treatment (18). *Hanley et al* (2010) stated that the fixed dose of enoxaparin may not be the most appropriate approach from a pharmacokinetic point of view, and clinically-focused studies will be required to determine which of these options may yield optimal clinical outcomes.

5. Summary

At the time of writing, there was no full-scaled, controlled prospective study found to compare weight-base and fixed prophylactic dosing strategies for enoxaparin. There is no sufficient evidence to support or negate the current enoxaparin health outcomes in obese and very obese patients due to the lack of post-discharge follow-up from hospitals. Further research is required to compare patients' long-term clinical outcomes after fixed and weigh-based dosing of enoxaparin. The optimal dose per kilogram of body weight for prophylactic enoxaparin regime will need to be determined.

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