Pharmacodynamics of low molecular weight heparin in patients undergoing bariatric surgery: A prospective, randomised study comparing two doses of parnaparin (BAFLUX STUDY)

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Background: The optimal dose of low-molecular-weight-heparin (LMWH) to prevent venous thromboembolism (VTE) after bariatric surgery remains controversial.

Aim: The aim of this study was to evaluate the pharmacodynamic parameters of two doses of the LMWH parnaparin administered to patients undergoing bariatric surgery.

Methods: Patients were enrolled in a multicentre, open label, pilot study and were randomised to receive 4250 IU/day [n=36; 30 females; median age: 38 years (23-56); median BMI: 46.7 Kg/m² (36.5-58.8)] or 6400 IU/day [n=30; 24 females; median age: 42 years (22-63); median BMI: 43.7 Kg/m² (36.1-64.1)] of parnaparin s.c. for 7-11 days. The pharmacodynamic effects of parnaparin were analysed by measuring the anti Factor Xa activity on day 0 (12 hours after the first parnaparin injection), day 4 and day 6 after surgery (before and 4 hours after parnaparin administration).

Results: In 98.3% of patients receiving 4250 IU/day the peak anti-Xa levels were in the range of 0.1-0.4 IU/ml. Higher anti-Xa levels were observed in patients receiving 6400 IU/day: in 62.3% of these patients the peak anti-Xa levels were greater than 0.4 IU/ml. The anti-Xa levels measured 4 hours after injection on days 4 and 6 were not statistically correlated with BMI for either dose of parnaparin (p=0.077 and p=0.401 for 4250 or 6400 IU/day, respectively).

Conclusion: The dose of 4250 IU/day seems adequate to achieve prophylactic anti-Xa levels in morbid obese patients undergoing bariatric surgery. Conversely, most of the patients receiving 6400 IU/day show anti-Xa levels higher than the recommended prophylactic values.

Introduction

Recent studies have shown that venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) is an important and frequent complication after bariatric surgery [1]. Reported rates of post-operative DVT and/or PE range from 1% to 15% despite prophylaxis [2-7] and about 50% of deaths occurring in bariatric patients are attributed to a fatal PE [8]. Therefore, prevention of VTE is crucial in this clinical setting and various regimens of low-molecular-weight heparin (LMWH) are used for peri-operative thromboprophylaxis [9-14]. However, there are no clear guidelines regarding the optimal dosage of LMWH to prevent VTE in morbid obese patients. Studies evaluating the weight-based dosage of LMWH are limited and criteria for dose adjustment in obese patients are not well established [15]. In particular, given that the intravascular volume does not have a linear relationship with body weight [16-18], it is possible that the use of weight-based dosing in obese patients could lead to overdosing; conversely, the use of a fixed thromboprophylactic dose could result in underdosing, while the safety and efficacy of a fixed intermediate dose has not been adequately investigated. The latest guidelines of the American College of Chest Physicians suggest anti-Xa monitoring when administering weight-based doses of LMWH to obese patients who weigh >150 kg [19,20];
however, the relationship between anti-Xa levels and clinical outcomes (VTE and haemorrhagic events) is still unclear.

Several studies performed in the general population have shown that the prophylactic range for anti-Xa activity levels for the prevention of VTE in surgical and non-surgical patients should be 0.1–0.4 U/ml [21–24]. Although monitoring of anti-Xa levels is not routinely required for patients receiving LMWH, the measurement of these levels has been suggested in obese patients; on the other hand, data in the specific setting of bariatric surgery are lacking [19,20].

We therefore performed a pilot, randomised, controlled, open-label study investigating the anti-Xa activity after a fixed prophylactic dose of parnaparin (4250 IU/day) or a fixed intermediate dose of parnaparin (6400 IU/day) in obese patients undergoing bariatric surgery. 4250 IU/day of parnaparin is the currently recommended dose for the prevention of VTE in high risk general surgery [25], while 6400 IU/day is slightly higher than the 25% increase of the standard dose for the prevention of VTE in surgical and non-surgical patients should be [26]. Before surgery, patients performed blood chemistry screening including Prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen, creatinine, aminotransferases, haemoglobin level and platelet count. Venous blood samples for anti-Xa measurement were collected by separate venipunctures on day 0 (the day of surgery, 12 hours after the first parnaparin injection), days 4 and 6 after surgery [before parnaparin injection (T0) and after 4 hours (T4)]. Anti-Xa activity measurement was centralised.

The study was approved by the Italian Health Authorities and by the local ethics committees; written informed consent was obtained from all patients. The study was initiated in 2004 prior to mandatory clinical trials registration, and the study was therefore not registered in a clinical trials registry [26].

Blood sampling and measurement of anti-Xa activity

Blood was collected from the antecubital vein into vacuum tubes (Becton and Dickinson, Meylan, France) containing trisodium citrate (0.109 M) as anticoagulant at a proportion 1:9. Plasma was prepared by centrifugation for 20 min at 2000 g at room temperature; platelet poor plasma was harvested, divided into coded plastic tubes, snap frozen and stored locally at −70 °C. Frozen aliquots were then sent by courier in dry ice to the centre where the anti-Xa activity was measured. Frozen plasma aliquots were stored at −70 °C until further processing. Plasma was thawed rapidly (5 minutes) in a water-bath at 37 °C before use.

The pharmacodynamic effects of parnaparin were analysed by measuring the anti Factor Xa (anti-Xa) activity using a chromogenic assay (HemosIL Heparin; Instrumentation Laboratory, Milan, Italy) and the results were expressed as IU anti-Xa/ml. The HemosIL Heparin assay is based on a synthetic chromogenic substrate and Factor X inactivation. Heparin is analyzed as a complex with the antithrombin present in plasma samples; the concentration of this complex is dependent on the availability of antithrombin. In order to obtain a constant antithrombin concentration, purified antithrombin is added to the test plasma. Factor X is then added in excess and is neutralised by the heparin–antithrombin complex. Residual Factor X is quantified using the synthetic chromogenic substrate. The parnaparin solution is monitored kinetically at 405 nm and is inversely proportional to the heparin level present in the plasma sample. Since different kinds of heparin have their own specific anti-Xa activity, parnaparin was used to perform the calibration curve (lot n.1593 exp 02/08). For the preparation of the calibration curve 3 standards of parnaparin at known concentrations were used (12, 0.6

Table 1
Baseline characteristics of enrolled patients.

<table>
<thead>
<tr>
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<th>Parnaparin 4250 IU/day</th>
<th>Parnaparin 6400 IU/day</th>
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<tbody>
<tr>
<td>Number</td>
<td>36</td>
<td>30</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>6/30</td>
<td>6/24</td>
</tr>
<tr>
<td>Age, years [median (range)]</td>
<td>38 (23–56)</td>
<td>42 (22–63)</td>
</tr>
<tr>
<td>BMI, Kg/m² [median (range)]</td>
<td>46.7 (36.3–58.8)</td>
<td>43.7 (36.1–64.1)</td>
</tr>
<tr>
<td>Creatinine clearance, ml/min *</td>
<td>92.85 (16.75)</td>
<td>86.65 (14.41)</td>
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</table>

* Calculated according to MDRD formula [32]; ** SD: standard deviation.
and 0 IU anti-Xa/ml). The calibration curve was included in each test run. Intra-assay variation was 3.6% and 3.5% and the run-to-run variation was 8.3% and 4.9% for plasma samples containing heparin at concentrations of 0.4 and 0.8 IU anti-Xa/ml, respectively.

The test was performed on an ACL instrument (Instrumentation Laboratory) by technicians blinded to the clinical characteristics and the dose of parnaparin given to the patients.

**Statistical analysis**

Continuous variables are presented as medians and ranges; the non-parametric Mann-Whitney U-test and Wilcoxon test were used for group comparison (unpaired and paired test, respectively). Spearman correlation coefficients and 95% confidence intervals (CI) were calculated to determine the association between variables.

A two-sided p value equal to or less than 0.05 was considered statistically significant. The SPSS statistical software package (Version 11.0, Chicago, Ill, USA) was used for data processing.

In the absence of data on the pharmacodynamics of LMWH in bariatric surgery, we chose a pre-planned analysis of the first 60 patients enrolled as sample of convenience.

**Results**

Between April 2004 and February 2007, 66 consecutive morbid obese patients (BMI > 36) undergoing bariatric surgery were enrolled in this study. There were 12 males and 54 females aged 22 to 63 years (median age: 39.1 years), with a BMI of 36.1 to 64.1 kg/m² (median BMI 44.8 kg/m²). After randomisation 36 patients received 4250 IU parnaparin/day and 30 patients 6400 IU parnaparin/day. Baseline characteristics of the patients are reported in Table 1; no statistically significant differences were found between the two groups. In Fig. 1 the correlation between factor Xa activity and creatinine is shown.

During the treatment period, anti-Xa activity levels significantly increased 4 hours after dosing (T4) compared with basal levels (T0) on both day 4 and day 6; the increase in anti-Xa activity levels was dose-response related (Table 2). Notably, in 98.3% of patients receiving 4250 IU/day the anti-Xa levels at peak were within the prophylactic range (0.1-0.4 IU/ml). Conversely, higher anti-Xa levels were observed in patients receiving 6400 IU/day; in 62.3% of these patients anti-Xa activity levels at peak were higher than 0.4 IU/ml. In both groups residual anti-Xa activity was still measurable 12 hours after the first pre-operative administration of parnaparin (Day 0); of interest, none of the patients receiving 6400 IU/day demonstrated anti-Xa levels greater than 0.4 IU/ml (Table 2).

Finally, the anti-Xa levels measured 4 hours (T4) after injection on days 4 and 6 were not significantly correlated with BMI for either parnaparin dosage [Spearman correlation coefficients: -0.232 (95% CI: -0.467–0.034; p=0.077) and -0.118 (95% CI: -0.383–0.166; p=0.401) in patients receiving parnaparin 4250 IU/day and 6400 IU/day, respectively]. Fig. 2 shows the anti-Xa levels measured at peak (T4) on days 4 and 6 according to the BMI value (≤45 vs >45 kg/m²) and the prophylactic regimen (4250 vs. 6400 IU/day of parnaparin). No statistically significant differences were found between subjects with a BMI ≤45 and those with a BMI >45 kg/m² for either dose of parnaparin (p = 0.111 and p = 0.737 for patients receiving 4250 and 6400 IU/day parnaparin, respectively).

**Discussion**

The appropriate prophylactic dosage of LMWH for VTE prevention in patients undergoing bariatric surgery is still a matter of debate [9–13,19,20].

In this study we compared the pharmacodynamic parameters of two different fixed doses of parnaparin. The results of our study suggest that a standard prophylactic dose of parnaparin (4250 IU/day) could be adequate to achieve prophylactic anti-Xa levels in morbid obese patients, while in most patients a higher dose (6400 IU/day) results in higher anti-Xa levels than those usually recommended for prophylaxis. The relationship between the dose of parnaparin and the levels of anti-Xa activity have been evaluated in non-obese patients, showing that mean anti-Xa levels 4 hours after administration of 4250 IU/day and 6400 IU/day were 0.27 IU/ml and 0.58 IU/ml, respectively [25]. Interestingly, these results are comparable to those reported in other studies performed with parnaparin in obese populations [27,28]. If we consider the effect of body weight on the dose of parnaparin, obese patients in our study received approximately 60% of the dose that a patient weighing 70–80 kg usually receives. Despite this, our results demonstrate that increasing the parnaparin dose to fill this hypothetical gap produced an excess of anticoagulant activity, suggesting that the higher doses recommended for VTE prophylaxis may increase the risk of bleeding without reducing the risk of thrombosis [19].

Moreover, the anti-Xa activity measured at peak was not significantly correlated with BMI for either parnaparin dose, suggesting a lack of correlation between total body weight and anti-Xa levels. This finding is

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**Table 2**

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<thead>
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<th>Parnaparin 4250 IU/day</th>
<th>Parnaparin 6400 IU/day</th>
<th>P</th>
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<tbody>
<tr>
<td>Day 0</td>
<td>0.032 (0.0-0.132)</td>
<td>0.060 (0-0.130)</td>
<td>0.009</td>
</tr>
<tr>
<td>Day 4</td>
<td>0.001 (0-0.082)</td>
<td>0.023 (0.0-0.129)</td>
<td>0.0023</td>
</tr>
<tr>
<td>T4</td>
<td>0.166 (0.10-0.370)</td>
<td>0.412 (0.177-0.668)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day 6</td>
<td>0.027 (0-0.086)</td>
<td>0.027 (0-0.086)</td>
<td>0.0001</td>
</tr>
<tr>
<td>T4</td>
<td>0.193 (0.120-0.453)</td>
<td>0.454 (0.126-0.729)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Between T0 and T4 for both days and both groups p < 0.0001.
in agreement with the results of two studies assessing therapeutic doses of dalteparin [29] and a prophylactic dose of nadroparin [30] in obese patients, and is in contrast with the results of other studies [15,31] that suggested the need to adjust the dosage of LMWH according to body weight. Our results are also consistent with those reported in two recently published studies on the pharmacodynamic activity of parnaparin in bariatric patients. In a small study of twenty patients undergoing surgery for severe obesity Legnani and colleagues showed that a fixed prophylactic dose of parnaparin (4250 IU/day) was able to achieve prophylactic anti-Xa levels, while a higher dosage (6400 IU/day) was associated with excessive anti-Xa levels in more than 80% of patients [27]. Forestieri and co-workers demonstrated in a small series of ten severely obese patients (BMI > 50 kg/m²) that doses of both 4250 IU/day and 6400 IU/day of parnaparin may provide effective prophylaxis for VTE in the peri-operative period; the authors speculated that higher doses, which may be associated with higher rates of bleeding complications, would offer no real improvement of efficacy [28].

This study has some limitations. Because of the small sample size and the relatively wide range of variability of anti-Xa levels, the results of our study must be interpreted with caution and definitive conclusions cannot be drawn about what anti-Xa levels could be reasonably expected in obese patients treated with different doses of parnaparin. However, this is, to our knowledge, the largest study ever published on the pharmacodynamic activity of LMWH in morbid obese patients; moreover, the practical difficulties associated with obtaining suitable patients for research in bariatric surgery make our results, albeit limited, of interest. Finally, the clinical consequences of these suggestions are debatable, since the relationship between anti-Xa levels and the occurrence of thrombotic complications is still not clear-cut [8]; consequently, in our study the efficacy and safety of either dose of LMWH has not been established and will be definitively clarified only at the conclusion of the large, currently ongoing clinical trial.

In conclusion, our study suggests that a dose of 4250 IU/day of parnaparin is adequate to achieve prophylactic anti-Xa levels in obese patients with a BMI > 36 Kg/m². On the other hand, the administration of a higher dose (6400 IU/day) produces anti-Xa levels higher than the recommended prophylactic values. The efficacy and safety of 4250 IU/day of parnaparin for VTE prophylaxis in bariatric surgery now strongly requires further investigation in larger randomised controlled trials with clinical end-points, before its validation for daily clinical practice.

Appendix A. Participating investigators and study sites

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References
