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Full Length Article

# The incidence of heparin-induced thrombocytopenia in patients treated with low molecular weight heparin for superficial vein thrombosis

Michelangelo Sartori *, Elisabetta Favaretto, Ludovica Migliaccio, Giuliana Guazzaloca, Cristina Legnani, Gualtiero Palareti, Benilde Cosmi

*Department of Angiology and Blood Coagulation, S. Orsola-Malpighi University Hospital, 40138 Bologna, Italy*

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ABSTRACT

*Background:* The risk of heparin induced thrombocytopenia (HIT) associated with low molecular weight heparin (LMWH) for treatment of superficial vein thrombosis (SVT) is uncertain. As a result the necessity of platelet count monitoring is unclear in this setting.
*Aims:* To assess the risk of HIT in outpatients treated with LMWH for SVT.
*Methods:* In a prospective single centre study we included all symptomatic outpatients in whom a real-time B-mode and color Doppler ultrasonography examination revealed SVT without DVT. Patients treated with vitamin K antagonists or fondaparinux were excluded. Patients received full dose enoxaparin for 1 week followed by half therapeutic dose for 3 weeks or parnaparin 8500 UI aXa for 10 days followed by 6400 UI aXa once daily for 20 days. Platelet count was performed on the day of diagnosis (D0) and 7 (D7), and 14 (D14) days afterward. Primary outcomes were the rate of thromboembolic events and of HIT during a 3-month follow-up.
*Results:* 678 outpatients (age: 64.7 ± 16.2 years, male: 42.0%) were evaluated. During follow-up, 7 venous thrombo-embolic events were recorded (1.03% CI 95%: 0.50–2.11%), while no major bleeding was observed (0.0% CI 95%: 0.0–0.56%). Platelet count was 255 ± 93 × $10^9$/L at D0, 245 ± 93 × $10^9$/L at D7 ($p = 0.204$ vs. D0) and 261 ± 116 × $10^9$/L at D14 ($p = 0.405$ vs. D0). No fall in platelet count > 50% and no case of HIT were recorded (HR 0.0% CI 95%: 0–0.56%).
*Conclusions:* A 4-week LMWH treatment for SVT is associated with an incidence of HIT lower than 0.6% and platelet count monitoring may be omitted in this setting.



## 1. Introduction

Superficial vein thrombosis (SVT) is a relatively common disease and is often associated with thromboembolic events in the deep venous system [1]. Treatment ranges from fondaparinux, low molecular weight heparin (LMWH), unfractionated heparin (UFH), and non-steroidal anti-inflammatory agents (NSAIDs) [2]. Intermediate dose LWMH has been proposed and it is widely used for SVT treatment [3]. The main side effects of heparin treatment are bleeding and heparin induced thrombocytopenia (HIT). HIT is an immuno-mediated adverse reaction to heparin due to the development of IgG against platelet factor 4–heparin complexes with platelet activating effects with thrombocytopenia and paradoxical thrombotic complications [4]. HIT mortality rate is high, regardless of therapy, and thromboembolic complications develop in approximately 50% of patients with confirmed HIT [5]. On the other hand, SVT is associated with low mortality and it has been considered to be a minor, benign, and self-limiting disease, requiring only symptom relief [3] and a more aggressive treatment with anticoagulants only in case of a significant thrombus burden (>4–5 cm in length) [3]. Thus, the efficacy of anticoagulants such as LMWH for SVT therapy should be balanced against the risks, such as bleeding and HIT. In medical and obstetrical patients receiving prophylactic LMWH, HIT appears to be rare (<0.1%) [6], and no episodes of major bleeding or HIT were observed in two studies which included LMWH at different dosages for SVT [7, 8]. However, the risk of HIT associated with LMWH treatment for SVT is uncertain. The aim of the present study was to assess the risk of thromboembolic events and of HIT in outpatients treated with LMWH for SVT.

## 2. Materials and methods

### 2.1. Study Design

A prospective cohort observational study was conducted in a tertiary care teaching hospital (S. Orsola-Malpighi University Hospital, Bologna, Italy). The study was approved by the institutional ethics committee. Patients provided informed consent according to the Declaration of Helsinki.

Symptomatic outpatients referred by general practitioners to the vascular emergency room for suspected acute SVT of the upper or

* Corresponding author at: Department of Angiology and Blood Coagulation, S. Orsola-Malpighi University Hospital, Pad. 2, Via Albertoni, 15, 40138 Bologna, Italy.
*E-mail address:* michelangelo.sartori@aosp.bo.it (M. Sartori).

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lower extremities were eligible. Each patient underwent: a) medical history and physical examination; b) ultrasonography of both lower limbs or of the symptomatic upper extremity by a vascular medicine physician as previously described [9–10]. Ultrasonography investigation was carried out with an EnVisor C HD instrument (Philips Medical System S.p.A., Monza, Italy). Patients were enrolled in case of objectively confirmed SVT diagnosis during business days and full blood count and creatinine levels measurements were performed before starting treatment. Patients were excluded if younger than 18 years, pregnant or in puerperium, with established diagnosis of concomitant deep vein thrombosis or symptoms attributable to pulmonary embolism, with life expectancy of <3 months, who were undergoing radiotherapy or chemotherapy, or had clinical or laboratory findings compatible with disseminated intravascular coagulation, sepsis, liver cirrhosis, chronic renal failure with creatinine clearance < 30 ml/min and who were treated with anticoagulant agents other than LMWH. Patients were also excluded in case of SVT located within 3 cm of the sapheno-femoral junction because they were treated with enoxaparin 1 mg/kg subcutaneously twice daily for at least five days and concurrent overlapping VKA, which were continued alone when the International Normalized Ratio (INR) was >2.0 for at least two days, with a target INR of 2.5 [11].

All other included patients received either full dose enoxaparin for 1 week followed by half therapeutic dose enoxaparin for 3 weeks according to the American College of Chest Physicians Evidence-Based Clinical Practice Guidelines of 2008 [12] or parnaparin 8500 UI aXa for 10 days followed by 6400 UI aXa once daily for 20 days (intermediate dose of LMWH for 30 days), according to the treatment schedule of the STEFLUX study [8]. In case of SVT of the lower limbs, patients were encouraged to use graduated compression stockings (23–32 mm Hg at the ankle), either knee or thigh high according to SVT location. Patients were allowed to take acetaminophen or topical NSAIDS for a week and were seen at 7 (D7), and 14 (D14) days after enrolment. At least three months after enrollment, patients were contacted by telephone or were seen at our outpatient clinic. Study outcome was the cumulative 3-month incidence of venous thromboembolism and of HIT, while the secondary outcome was recurrent SVT and major bleeding.

In case of worsening symptoms and/or suspected venous thromboembolism (VTE) the patients were encouraged to refer to our outpatient service and underwent: a) ultrasonography of whole leg (the results of which were compared with the previously available exam) or of the symptomatic upper limb b) a blood sample for platelet count. Patients with symptoms of pulmonary embolism had diagnostic testing based on pretest clinical probability, D-dimer and multidetector CT scan. A blood sample for platelet count was also taken.

### 2.2. Platelet count monitoring and HIT diagnosis

A platelet count was performed on the day of diagnosis (D0), on D7, and D14 and in case of worsening symptoms and/or suspected VTE. HIT was suspected in all cases of a 50% or more drop in platelet count in comparison to the pretreatment value or any further platelet count drop during heparin therapy. In case of a platelet count drop of 50% or more, a blood sample was obtained for the determination of heparin-dependent IgG antibodies. HIT was diagnosed in case of a positive IgG specific ELISA (PF4 Enhanced IgG, Immucor GTI Diagnostics, Inc.) confirmed by a platelet aggregation test, as previously described [13].

### 2.3. Statistical analysis

Analysis was carried out using the SPSS™ software package (version 15.0; SPSS Inc. Chicago, Illinois, USA). Categorical variables were expressed as frequency and percentage with 95% confidence interval; continuous variables were expressed as mean ± standard deviation (SD) with inter-quartile ranges (IQR). Student's *t*-test and multivariate analysis of variance with Bonferroni's correction for multiple comparisons were used to compare means among groups. Cumulative end-point curves were estimated with the Kaplan-Meier procedure. The significance level was two sided and set at $\alpha = 0.05$.

## 3. Results

The study was performed from 1 Jan 2012–01 June 2015. Characteristics of the enrolled patients (n = 678) are summarized in Table 1. The majority of patients had lower extremity SVT (Table 1). The most frequent risk factors for SVT were the presence of varicose veins and a previous superficial or deep vein thrombosis (Table 1). Cancer was present in 5.3% of the study population (Table 1). The majority of patients were treated with enoxaparin (n = 621, 91.6%), all the others with parnaparin.

As reported in Fig. 1, platelet count was 255 ± 93 × $10^9$/L at D0, 245 ± 93 × $10^9$/L at D7 (p = 0.204 vs. D0) and 261 ± 116 × $10^9$/L at D14 (p = 0.405 vs. D0). No patient had a fall in platelet count > 50%, 4 patients (0.59% CI 95%: 0.23–1.51%) had a platelet fall between 40% and 50%, 10 patients (1.47% CI 95%: 0.80–2.69%) had a platelet fall between 30% and 40%.

During 3-month follow-up, no major bleeding was observed (0.0% CI 95%: 0.0–0.56%), whereas 7 thromboembolic events (6 deep vein thrombosis and one pulmonary embolism, no arterial thromboembolic events) were recorded (1.03% CI 95%: 0.50–2.11%) and 29 recurrent SVTs were observed (4.28% CI 95%: 3.0–6.08%). No patient had VTE during the 4-week treatment with LMWH and all the four patients with platelet fall between 40% and 50% had no events during follow-up. The cumulative incidence of SVT and/or VTE during follow-up is reported in Fig. 2. In all the patients with recurrent SVT or VTE (n = 36, 5.31% CI 95%: 3.86–7.26%), platelet count on the day of recurrent SVT or on the day of VTE diagnosis was similar to D0 (i.e. a fall in platelet count < 25% in comparison to D0), except for a patient with a drop in platelet fall of 41%. He did not undergo a heparin-dependent IgG antibodies assay since he had a recurrent SVT after 56 days from the last injection of enoxaparin (i.e. 84 days from the enrollment). Patients with deep vein thrombosis and pulmonary embolism were treated with enoxaparin 1 mg/kg subcutaneously twice a day and VKA with a target International Normalized Ratio (INR) of 2.5 without any other further thromboembolic event in the following weeks. Patients with recurrent SVT were treated with therapeutic doses of LMWH without any other further thromboembolic event in the following weeks. In conclusion, no HIT case was observed during the three-month follow-up (HR 0.0% CI 95%: 0–0.56%).

## 4. Discussion

Our study shows that a 4-week course of LMWH for SVT is associated with a low risk of HIT and such risk is similar to that of medical patients receiving prophylactic LMWH doses.

HIT occurs most commonly in certain patient populations, such as postoperative patients who receive UHF [6], whereas in several patient groups the risk of HIT can be classified as "uncommon" (i.e., 0.1 to 1%). A meta-analysis of studies enrolling surgical and medical patients who received prophylaxis showed a lower incidence among those who

**Table 1**
Characteristics of the study population (n = 678).

| | |
|---|---|
| Age ± SD (IQR) | 64.7 ± 16.2 years (52–77) |
| Male (%) | 285 (42.0) |
| Upper extremity SVT (%) | 71 (10.5) |
| Lower extremity SVT (%) | 607 (89.5) |
| Varicose vein (%) | 430 (63.4) |
| Active cancer (%) | 36 (5.3) |
| History of vein thrombosis[a] (%) | 194 (28.6) |
| Oestrogen-containing therapy[b] (%) | 12 (1.8) |

[a] Superficial or deep vein thrombosis.
[b] Contraceptive or hormone replacement.