CHEST

Original Research

ANTITHROMBOTIC THERAPY

No Difference in Risk for Thrombocytopenia During Treatment of Pulmonary Embolism and Deep Venous Thrombosis With Either Low-Molecular-Weight Heparin or Unfractionated Heparin*

A Metaanalysis

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Background: **Low-molecular-weight heparin (LMWH) is a popular alternative to unfractionated heparin (UH) for the treatment of pulmonary embolism (PE) and deep vein thrombosis (DVT), in part based on the perception of a lower risk for heparin-induced thrombocytopenia (HIT). To investigate the evidence supporting this perception, we performed a metaanalysis to compare the incidence of thrombocytopenia between LMWH and UH during PE and/or DVT treatment.**

Methods: **Randomized trials comparing LMWH with UH for PE and/or DVT treatment were searched for in the MEDLINE database, bibliographies, and by correspondence with published investigators. Two reviewers independently selected high-quality studies and extracted data regarding heparin-associated thrombocytopenia (HAT), HIT confirmed by laboratory testing, and heparin-induced thrombocytopenia with thrombosis (HITT). Outcome rates between LMWH and UH were compared using a binomial, generalized linear mixed model with a logit link and Gaussian random effects for study.**

Results: **Thirteen studies involving 5,275 patients met inclusion criteria. There were no statistically significant differences in HAT rates between the two treatments (LMWH, 1.2%; UH, 1.5%; p = 0.246). The incidence of documented HIT and HITT was too low to make an adequate comparison between groups.**

Conclusions: **Our review disclosed no statistically significant difference in HAT between LMWH and UH and insufficient evidence to conclude that HIT and HITT rates were different between them. There was no evidence from randomized comparative trials to support the contention that patients receiving treatment for PE or DVT with UH are more prone to these complications than those receiving LMWH.** ***(CHEST 2007; 132:1131–1139)***

Key words: deep vein thrombosis; heparin-associated thrombocytopenia; heparin-induced thrombocytopenia; heparin-induced thrombocytopenia with thrombosis; low-molecular-weight heparin; pulmonary embolism; unfractionated heparin

Abbreviations: CI = confidence interval; DVT = deep vein thrombosis; HAT = heparin-associated thrombocytopenia; HIT = heparin-induced thrombocytopenia; HITT = heparin-induced thrombocytopenia with thrombosis; LMWH = low-molecular-weight heparin; OR = odds ratio; PE = pulmonary embolism; PF4 = platelet factor 4; UH = unfractionated heparin; VTE = venous thromboembolism

The choice between unfractionated heparin (UH) and low-molecular-weight-heparin (LMWH) for the treatment of patients with pulmonary embolism (PE) or deep vein thrombosis (DVT) is controversial. Both classes of drugs have comparable efficacy and safety,[1] and data suggest that both are safe and effective for outpatient, subcutaneous administration without laboratory monitoring.[2] However, there is a

perception among clinicians that treatment with LMWH entails a lower risk than UH of thrombocytopenia and the devastating complication of heparin-induced thrombocytopenia with thrombosis (HITT). We undertook this metaanalysis to compare objectively the incidence of these complications in patients treated for venous thromboembolism (VTE) with either LMWH or UH.

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One metaanalysis[1] of VTE treatment trials published 6 years ago disclosed no significant difference in the rates of thrombocytopenia development between LMWH and UH. However, that metaanalysis was limited to studies that compared subcutaneous LMWH to IV UH on the basis of recurrent thromboembolism and bleeding. Their inclusion criteria primarily concerned how these two outcomes were objectively assessed. Furthermore, subsequent recommendations for the treatment of VTE continue to be premised on the assumption that LMWH have a lower risk of thrombocytopenia than UH and extend to the recommendation that less-frequent platelet monitoring is necessary with LMWH than it is with UH.[3]

In order to define the relative risk of thrombocytopenia optimally between UH and LMWH for the initial treatment of PE and DVT, we performed a metaanalysis of all randomized trials that compared the two drug types for this indication. The primary outcome we used for our study selection and analysis was thrombocytopenia, including documented heparin-induced thrombocytopenia (HIT) as well as HITT during the initial treatment period.

Materials and Methods

Study Identification

A literature search was performed to identify the results of randomized control trials comparing the rates of thrombocytopenia between LMWH and UH during the treatment of VTE. A computerized search of the MEDLINE database was done for all references published between January 1985 and June 2006 using the following key words and terms: "deep vein thrombosis," "pulmonary embolism," "low molecular weight heparin" (including the varied formulations), "unfractionated heparin," "venous thromboembolic disease," "thrombosis," and "clinical trial." The list was limited to references in the English language.

Additional publications for evaluation were obtained from the references from all reviews and metaanalyses yielded by the original computer search. In addition, publishers of applicable articles were contacted to see if they knew of any relevant unpublished trials.

Study Selection

Criteria for study selection were defined prospectively. Two investigators independently evaluated studies for possible inclusion, and disagreements were resolved by discussion. To be included, studies had to be randomized control trials of patients with objectively diagnosed PE or DVT (*ie*, pulmonary angiography, contrast venography, duplex ultrasound, Doppler scan, ventilation-perfusion scan, and/or CT scanning). The studies were considered for inclusion if they compared UH to LMWH of any type, preparation, and route of administration for VTE treatment, provided that the planned follow-up was the same for UH and LMWH. The studies also needed to define thrombocytopenia objectively, screen and measure platelet counts, and compare rates of thrombocytopenia of LMWH with UH in the initial treatment of VTE.

For the purposes of primary analysis, an acceptable quantitative definition of "thrombocytopenia" during UH or LMWH therapy was predefined as the occurrence of platelet counts in the range of 80,000 to 120,000/μL or a decrease by at least 50% with respect to a previously measured platelet level. A secondary analysis included all definitions of thrombocytopenia specified in the respective articles. HIT was defined as thrombocytopenia during therapy, confirmed by an objective test for the disorder, such as a heparin-induced serotonin release assay, heparin-induced platelet aggregation, or heparin-platelet factor 4 (PF4) enzyme-linked immunosorbent assay. HITT was defined as thrombocytopenia occurring during treatment, along with objective evidence of a new thrombosis in a vein or artery.

Assessment of Study Quality

We used a modified version of the study quality criteria of Nurmohamed and colleagues[4] to evaluate the VTE treatment trials for inclusion in the metaanalysis. These criteria include the following: (1) randomized control trial; (2) inclusion and exclusion criteria clearly defined; (3) randomization clearly specified; (4) clinical characteristics of study group adequately described; (5) description of any bleeding complications; (6) accurate diagnosis of DVT/PE; (7) blinded end point assessment; (8) adequate description of patients not completing the protocol; and (9) routine platelet counts performed. A study was considered to be of high quality if it met at least eight of the nine prespecified criteria.

Data Extraction

Two investigators independently extracted data on study design, study quality, and the outcome of thrombocytopenia with each therapy. The data abstracted for each trial were confirmed by consensus. Using the pooled data from the accepted clinical studies, the absolute rates of thrombocytopenia in the LMWH group and the UH group were calculated.

Statistical Analysis

All calculations were performed using statistical software (R, version 2.0.1; R Core Development Team, R Foundation for

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