CLINICAL RESEARCH STUDY

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Low-molecular-weight or Unfractionated Heparin in Venous Thromboembolism: The Influence of Renal Function

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ABSTRACT

BACKGROUND: In patients with acute venous thromboembolism and renal insufficiency, initial therapy with unfractionated heparin may have some advantages over low-molecular-weight heparin.

METHODS: We used the Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) Registry data to evaluate the 15-day outcome in 38,531 recruited patients. We used propensity score matching to compare patients treated with unfractionated heparin with those treated with low-molecular-weight heparin in 3 groups stratified by creatinine clearance levels at baseline: >60 mL/min, 30 to 60 mL/min, or <30 mL/min.

RESULTS: Patients initially receiving unfractionated heparin therapy (n = 2167) more likely had underlying diseases than those receiving low-molecular-weight heparin (n = 34,665). Propensity score-matched groups of patients with creatinine clearance levels >60 mL/min (n = 1598 matched pairs), 30 to 60 mL/min (n = 277 matched pairs), and <30 mL/min (n = 210 matched pairs) showed an increased 15-day mortality for unfractionated heparin compared with low-molecular-weight heparin (4.5% vs 2.4% [P = .001], 5.4% vs 5.8% [P = not significant], and 15% vs 8.1% [P = .02], respectively), an increased rate of fatal pulmonary embolism (2.8% vs 1.2% [P = .001], 3.2% vs 2.5% [P = not significant], and 5.7% vs 2.4% [P = .02], respectively), and a similar rate of fatal bleeding (0.3% vs 0.3%, 0.7% vs 0.7%, and 0.5% vs 0.0%, respectively). Multivariate analysis confirmed that patients treated with unfractionated heparin were at increased risk for all-cause death (odds ratio, 1.8; 95% confidence interval, 1.3-2.4) and fatal pulmonary embolism (odds ratio, 2.3; 95% confidence interval, 1.5-3.6).

CONCLUSIONS: In comparison with low-molecular-weight heparin, initial therapy with unfractionated heparin was associated with a higher mortality and higher rate of fatal pulmonary embolism in patients with creatinine clearance levels >60 mL/min or <30 mL/min, but not in those with levels between 30 and 60 mL/min.

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KEYWORDS: Low-molecular-weight heparin; Mortality; Renal insufficiency; Unfractionated heparin; Venous thromboembolism

Current guidelines of antithrombotic therapy recommend that patients with acute venous thromboembolism be treated initially with low-molecular-weight heparin or fondaparinux over unfractionated heparin.[1,2] Low-molecular-weight heparin has the advantage that it is easier to administer than unfractionated heparin (which makes outpatient treatment

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*A full list of RIETE Investigators is given in the Appendix.

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feasible) and has a lower potential for heparin-induced thrombocytopenia,[3] but the disadvantage is that it accumulates in patients with renal failure. In the setting of severe renal insufficiency, use of unfractionated heparin may avoid the problems associated with impaired clearance of low-molecular-weight heparin preparations. Moreover, an increasing body of evidence supports renal insufficiency as an independent risk factor for major bleeding but also for venous thromboembolic events in patients receiving anticoagulant treatment.[4-10]

Patients with severe renal insufficiency are often excluded from randomized clinical trials of anticoagulant therapy, which means that treatment regimens based on the results from clinical trials might not be suitable for these patients. The former guidelines from the American College of Chest Physicians suggested that in patients with severe renal failure (creatinine clearance levels <30 mL/min), unfractionated heparin should be preferred over low-molecular-weight heparin because it is not eliminated by the kidney (grade 2C), and that low-molecular-weight heparin should be administered with care and their dose adjusted to anti-Xa level.[11,12] Current guidelines suggest that if low-molecular-weight heparin is chosen, anti-Xa monitoring or dose reduction should be considered to ensure that there is no accumulation.[13]

The Registro Informatizado de la Enfermedad TromboEmbólica (RIETE) is an ongoing, international (Spain, Italy, France, Israel, Switzerland, Germany, Republic of Macedonia, Greece, Czech Republic, and Ecuador), multicenter, prospective registry of consecutive patients presenting with symptomatic, acute venous thromboembolism. Data from this registry have been used to evaluate outcomes after acute venous thromboembolism, such as the frequency of recurrences, bleeding and mortality, and risk factors for these outcomes.[9,14] The current analysis compares the mortality rate, the rate of fatal pulmonary embolism, and the rate of fatal bleeding during the first 15 days after diagnosis in patients receiving initial therapy with unfractionated heparin versus low-molecular-weight heparin, according to different levels of renal function at baseline. We were especially interested in determining whether patients with venous thromboembolism with creatinine clearance levels <30 mL/min receiving low-molecular-weight heparin therapy had a higher mortality than those treated with unfractionated heparin.

CLINICAL SIGNIFICANCE

- The superiority of low-molecular-weight heparin over unfractionated heparin in patients with venous thromboembolism and normal renal function has been demonstrated in randomized clinical trials.
- Among patients with severe renal failure, those initially treated with unfractionated heparin had a 2-fold higher mortality than those receiving low-molecular-weight heparin, with no differences in bleeding.
- Multivariate analysis confirmed that patients receiving unfractionated heparin had an increased mortality irrespective of renal function.

MATERIALS AND METHODS

Study Population

Consecutive patients with symptomatic, acute deep vein thrombosis or pulmonary embolism, confirmed by objective tests (contrast venography or ultrasonography for suspected deep vein thrombosis; pulmonary angiography, lung scintigraphy, or helical computed tomography scan for suspected pulmonary embolism), were enrolled in the RIETE. Patients were excluded if they were currently participating in a therapeutic clinical trial with a blinded therapy. All patients provided written or oral consent for participation in the registry, in accordance with local ethics committee requirements.

In the RIETE Registry, participating physicians ensured that eligible patients were consecutively enrolled. Data were recorded in a computer-based case report form at each participating hospital and submitted to a centralized coordinating center through a secure website. The study coordinating center assigned patients with a unique identification number to maintain patient confidentiality and was responsible for all data management. Data quality was regularly monitored electronically, including checks to detect inconsistencies (>60, 30-60, or <30) or errors, which were resolved by the local coordinators. Data quality also was monitored by periodic visits to participating hospitals by contract research organizations that compared medical records with the submitted data.

Design of the Analysis

Patients were categorized into 3 groups according to creatinine clearance levels at baseline (>60, 30-60, or <30 mL/min), and outcomes were compared across these categories. Creatinine clearance levels were calculated according to the Cockcroft and Gault formula.[15] The major outcome was all-cause mortality within the first 15 days after diagnosis of venous thromboembolism. Secondary outcomes were the rate of fatal pulmonary embolism, fatal bleeding, recurrent thromboembolism, and major bleeding. Fatal pulmonary embolism, in the absence of autopsy, was defined as any death occurring within 10 days of recurrent pulmonary embolism (confirmed by objective tests) in the absence of any alternative cause of death. Fatal bleeding was defined as any death occurring within 10 days of a major bleeding episode in the absence of an alternative cause of death. Bleeding was classified as "major" if it was fatal, retro-