
Use of Low Molecular Weight Heparins in Patients With Acute Venous Thromboembolism

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TAKE HOME MESSAGE

There is sufficient evidence to conclude that, when compared with unfractionated heparin, low molecular weight heparins (LMWH) reduce both mortality and recurrences of venous thromboembolism (VTE) in patients with proximal deep vein thrombosis (DVT). Furthermore, the risk of hemorrhagic complications is also significantly reduced with LMWHs compared with unfractionated heparin. The benefit of LMWHs in pulmonary embolism is less clear.

OBJECTIVE

To determine whether low molecular weight heparins are superior to heparin therapy for the treatment of patients with venous thromboembolism.

DATA SOURCES

Trials were identified from the Cochrane Peripheral Vascular Diseases Group trials register and the Latin America and Caribbean Health Sciences Literature (LILACS). The reviewers contacted colleagues and representatives of pharmaceutical companies for additional information about trials. The review is updated to July 1999.

STUDY SELECTION

Studies were included if they were randomized, controlled studies comparing fixed-dose, subcutaneous LMWH with adjusted-dose, intravenous, or subcutaneous unfractionated heparin in adult patients with VTE.

DATA EXTRACTION

Two authors independently extracted the data and assessed the quality of the trials. The principal outcome measures were death, incidence of recurrent VTE, and the development of treatment-related side effects in the form of major bleeding episodes. Bleeding during the initial period was defined as “major” if it led directly to death, necessitated transfusion, or if it led to the interruption of antithrombotic treatment or surgical intervention. For each of these outcomes, results are expressed as an odds ratio (OR) with 95% confidence intervals (CIs). Specific subgroup analyses were conducted in patients with proximal DVTs only, in patients with confirmed pulmonary embolism, and in patients with (and without) malignant disease.

MAIN RESULTS

From 29 potentially eligible studies, 14 were included and involved 4,754 patients. Six different agents were studied in these 14 trials. Overall, many trials failed to use concealed allocation and, given the comparisons, most studies were not double-blinded; subgroup analyses were performed in attempts to examine the effect of these issues. By the end of the follow-up in 11 trials, thrombotic complications occurred in the same proportions in both groups (OR 0.76; 95% CI 0.57 to 1.01). Drawing on mortality data from the same trials, fewer patients treated with LMWH died compared with patients treated with unfractionated heparin (OR 0.78; 95% CI 0.62 to 0.99). This amounts to 16 fewer deaths for every 1,000 patients treated with LMWH who might have otherwise received unfractionated heparin. At the end of the initial treatment period, in all 14 trials, major hemorrhages occurred in fewer patients treated with LMWH compared with unfractionated heparin (OR 0.60; 95% CI 0.39 to 0.93).

Subgroup analysis of patients with proximal DVTs showed statistically significant reductions favoring LMWH in terms of recurrent VTE (OR 0.60; 95% CI 0.40 to 0.89), major hemorrhages (OR 0.44; 95% CI 0.21 to 0.95), and overall mortality (OR 0.64; 95% CI 0.43 to 0.93).

Patients with confirmed pulmonary embolism comprised only 18% of the patients in this review, and al-

though there appears to be no difference between unfractionated heparin and LMWH, the small numbers limit the strength of this conclusion. In an assessment of mortality at the end of follow-up in patients with malignancy and DVT, LMWH was associated with a significant reduction in the risk of death (OR 0.53; 95% CI 0.33 to 0.85).

CONCLUSIONS

LMWH is at least as effective as unfractionated heparin in preventing recurrent VTE and significantly reduces the occurrence of major hemorrhage during initial treatment and overall mortality at the end of follow-up. It can be adopted safely as the standard of care for DVT. Studies comparing individual LMWH against each other are merited. There is no conclusive evidence regarding the use of LMWH versus unfractionated heparin in the treatment of pulmonary embolism.

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COMMENTARY: CLINICAL IMPLICATION

Patients with symptoms compatible with VTE (DVT and/or pulmonary embolism) present commonly to an emergency department for assessment and treatment. The health care costs associated with this continuum of diseases are enormous, and guidelines for assessing¹ and treating² both DVT and pulmonary embolism have been developed. Therefore, treatments that improve outcomes for patients with VTE are an important contribution to the literature.

The evidence presented in this review is contributing to a new way patients with this frequently encountered condition are being managed. Traditional treatment for patients with DVT consisted of admission to hospital and treatment with unfractionated heparin until therapeutic levels of anticoagulation were achieved. Patients routinely required lengthy hospital stays and required multiple laboratory tests. Moreover, they were frequently discharged when their chronic anticoagulation parameters had not achieved therapeutic levels.

With their ease of administration (eg, subcutaneous injections, frequently once daily dosing), LMWH compounds offer the theoretical advantage of providing

antithrombotic therapy without the need for frequent monitoring of coagulation indices and, hence, the potential to avoid hospitalization. Despite the large number of agents available, this review has focused on the “class effect” of LMWHs and has suggested that the results observed apply to the class in general.

Given the evidence presented in this review, it appears that not only do LMWHs offer important practical and cost-saving advantages in terms of avoiding hospitalization, but they are also superior to unfractionated heparin in terms of efficacy and safety. However, it is worth noting that a large proportion of the patients in this review were still treated in the hospital and that the question of whether this condition can be safely treated on an outpatient basis is a separate, although related, question.³

In summary, the evidence presented here suggests that clinicians should strongly consider the use of this class of agents for patients with VTE. The evidence is clear for DVT, and LMWH should become the treatment of choice for this condition. Out-patient treatment of this disorder is now becoming more common practice in many centers.⁴ It is likely that the benefit of LMWHs is similar in pulmonary embolism; however, the small number of patients studied in this regard suggests that caution is warranted before recommending LMWH for all cases of VTE.

Intriguing data have also been published regarding the cost savings associated with LMWH treatment compared with unfractionated heparin.⁵ Overall, despite the initial higher costs associated with the purchase of LMWHs, their use is more cost effective than unfractionated heparin. The savings accrue from the reduction of laboratory costs and early and more common treatment of patients outside the hospital setting. The challenge for emergency physicians is to select appropriate patients for this treatment option and then connect these patients to health care providers who can closely monitor this condition.

EVIDENCE-BASED MEDICINE TEACHING POINTS

Heterogeneity. In systematic reviews, heterogeneity refers to the differences between (variability) studies in the estimated effects. Statistical tests can determine whether the degree of variability between studies is greater than that expected by chance. The validity of pooling data from studies that demonstrate significant heterogeneity is questionable, and results should be viewed with caution.

LILACS. This is an electronic science and medicine database of Latin American and Caribbean literature

maintained by the Pan American Health Organization. Using electronic database searches from multiple sources and using standardized approaches reduces the chance of missing important foreign language and nonmainstream publications.

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