

THERAPEUTICS

Fixed-dose, weight-adjusted, unfractionated heparin was as effective and safe as low-molecular-weight heparin for venous thromboembolism

Kearon C, Ginsberg JS, Julian JA, et al. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism. *JAMA*. 2006;296:935-42.

Clinical impact ratings: GIM/FP/GP ★★★★★☆ Hospitalists ★★★★★☆ Hematol/Thrombo ★★★★★☆

QUESTION

In patients with newly diagnosed venous thromboembolism (VTE), is fixed-dose, weight-adjusted, unfractionated heparin as effective and safe as low-molecular-weight (LMW) heparin?

METHODS

Design: Randomized controlled noninferiority trial.

Allocation: Concealed.*

Blinding: Blinded (outcome adjudication committee and monitoring committee).*

Follow-up period: 3 months.

Setting: 8 hospitals in Ontario and Quebec, Canada, and in New Zealand.

Patients: 708 patients ≥ 18 years of age (mean 60 y, 55% men) newly diagnosed with symptomatic (80% of patients) or asymptomatic (1%) deep venous thrombosis of the legs or symptomatic pulmonary embolism (19%). Exclusion criteria included recent acute treatment of VTE for > 48 hours, long-term anticoagulant therapy, active bleeding, pregnancy, and creatinine level > 200 μmol/L (2.3 mg/dL).

Intervention: Unfractionated heparin (first dose 333 U/kg, subsequent doses 250 U/kg)

(*n* = 355) or LMW heparin (all doses 100 IU/kg) (*n* = 353). Both treatments were administered subcutaneously, twice daily, in fixed doses determined by patient weight and without use of coagulation tests to modify dose, for ≥ 5 days until the international normalized ratio (INR) was ≥ 2.0 for 2 consecutive days. Warfarin was started concurrently and continued for ≥ 3 months.

Outcomes: Recurrent VTE, major bleeding episode, and death.

Patient follow-up: 98% (intention-to-treat analysis).

MAIN RESULTS

Unfractionated heparin and LMW heparin did not differ for recurrent VTE, major bleeding, or death (Table).

Fixed-dose, weight-adjusted, unfractionated heparin vs low-molecular-weight heparin for acute treatment of venous thromboembolism (VTE)†

Outcomes	Follow-up	Unfractionated heparin	Low-molecular-weight heparin	Difference (95% CI)
Recurrent VTE	3 mo	3.8%	3.4%	0.4% (−2.6 to 3.3)‡
Major bleeding	10 d	1.1%	1.4%	−0.3% (−2.3 to 1.7)
Death	3 mo	5.2%	6.3%	−1.1% (−4.6 to 2.5)

†CI defined in Glossary.

‡Criterion for noninferiority was met because the upper limit of the CI was < 5%.

CONCLUSION

In patients with newly diagnosed venous thromboembolism (VTE), treatment with fixed-dose, weight-adjusted, unfractionated heparin resulted in rates of recurrent VTE and major bleeding similar to those with low-molecular-weight heparin.

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*See Glossary.

COMMENTARY

The trial by Kearon and colleagues is a landmark study. Many thanks to our Canadian colleagues (and the Heart and Stroke Foundation of Ontario) for the time, effort, and money needed to determine the appropriate dosing regimen for subcutaneous (SC) regular heparin (1) and to conduct a large multicenter clinical trial. The complete and thoughtful editorial by Dr. Jeff Carson in the same issue of *JAMA* should be read (2). Solid evidence now exists that regular heparin, administered subcutaneously in the doses described, is as effective and safe as LMW heparin in the initial treatment of acute VTE. Although confirmatory studies would be informative, it is unlikely that a pharmaceutical company or the U.S. Food and Drug Administration will ever select SC regular heparin as the comparator in future clinical trials of the new oral anticoagulants in the pipeline (3).

What will prevent widespread adoption of SC regular heparin? First, some physicians will undoubtedly feel that more evidence is needed in the form of more clinical trials. Second, the dosing may be somewhat alarming to many physicians who are used to giving a daily intravenous dose of regular heparin in the range of 20 000 to 40 000 IU. For a patient weighing 100 kg, one will now order a first dose of 33 000 IU of SC regular heparin and then 25 000 IU every 12 hours thereafter (50 000 IU/d). Third, regular heparin must be injected twice a day, whereas LMW heparin can be given once a day. Fourth, special populations were not studied. It may take years, as it did with LMW

heparin, to determine how to dose regular heparin in very overweight persons or patients with renal insufficiency. Fifth, no incidence of heparin-induced thrombocytopenia was reported, but this adverse effect is an important concern. The platelet count must be monitored at least every other day starting on day 4 (if the patient is heparin naïve) (4). Sixth, if a patient is sent home using SC heparin, pharmacies must be able to draw up the correct, highly concentrated doses of heparin, which must then be refrigerated. Seventh, if a new oral anti-coagulant emerges as an effective, safe alternative to heparin, followed by oral warfarin and INR monitoring, many physicians will opt for the easy-to-use oral drug.

The major benefit of SC regular heparin is its low cost. The savings could be substantial (2). Given the increasing number of people who have no health insurance or drug benefits, SC regular heparin represents an option for those who have to pay out-of-pocket.

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References

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3. Weitz JI. *Thromb Haemost*. 2006;96:274-84.
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