MINDFUL PRACTICE

Subcutaneous Unfractionated Heparin: Ready for Prime Time?

BY JON O. EBBERT, M.D., AND ERIC G. TANGALOS, M.D.

The Problem

A 52-year-old nurse with a history of breast cancer treated with mastectomy presents to you with a 3-day history of leg pain and swelling. She has calf tenderness and edema, and an ultrasound obtained that day shows an acute thrombus in the deep femoral vein. You plan to start her on low-molecular-weight heparin (LMWH) as an outpatient. One of her own patients recently received subcutaneous unfractionated heparin (UH), and she asks you to prescribe that for her because the copayment for the LMWH is prohibitive. You were not aware of this option and do an online, real-time search for the information.

The Question

In patients with deep vein thrombosis, does treatment with subcutaneous UH have comparable safety and efficacy to LMWH?

The Search

You go to PubMed (www.pubmed.gov) and enter "subcutaneous heparin" AND "pulmonary embolism," limiting the search to randomized controlled trials.

Our Critique

This study is an exciting and well-conducted clinical trial that is potentially ground-breaking for providing data on the safety and efficacy of subcutaneous UH for the outpatient treatment of venous thromboembolism. We have used this approach in our practice in appropriate situations (nursing home resident with advanced dementia and a no-hospitalization order), and it remains to be seen whether clinicians will adopt this practice. Because the trial's sample size was small, clinicians may want to wait for further studies before adopting this approach for widespread clinical practice.

Clinical Decision

You discuss the findings with your patient and express your lack of comfort with this approach at this time. You refer her to the physician in your area who prescribed UH for her patient.

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Fixed-Dose Heparin (FIDO) Investigators. Comparison of fixed-dose weight-adjusted unfractionated heparin and low-molecular-weight heparin for acute treatment of venous thromboembolism (JAMA 2006;296:935-42.)

▶ **Design and Setting:** This randomized, open-label, outcome adjudicator-blinded, noninferiority trial was conducted at university-affiliated clinical centers in Canada and New Zealand.

▶ **Subjects:** Potential subjects were 18 years of age or older with newly diagnosed deep vein thrombosis (DVT) of the leg or pulmonary embolism (PE). Symptomatic DVTs were diagnosed by compression ultrasonography or venography. Those symptomatic DVTs confined to the calf veins and asymptomatic DVTs required venographic diagnosis. PE was symptomatic and diagnosed by either high-probability ventilation/perfusion scan, nondiagnostic VQ scan associated with diagnostic findings for DVT, or CT scan. Patients were excluded if they were pregnant; were unable to complete follow-up assessments; or had contraindication to subcutaneous therapy, active bleeding, life expectancy less than 3 months, treatment for venous thromboemoblism (VTE) for more than 48 hours, long-term anticoagulation therapy, a contraindication to heparin or radiographic contrast, or creatinine greater than 2.3 mg/dL.

▶ **Intervention:** Patients received weight-adjusted, fixed-dose, twice-daily dosing of UH (intervention) or LMWH (control). Coagulation tests were not allowed, but a sample was obtained for each UH patient on the third day. UH was given in a dose of 333 U/kg followed by a second dose of 250 U/kg. LMWH was either dalteparin or enoxaparin and was given at 100 IU/kg for all doses. The LMWH or UH was given for at least 5 days and until the international normalized ratio was 2.0 or higher.

▶ **Outcomes:** The trial was designed to determine whether initial treatment with fixed-dose UH was as effective as LMWH. Subjects were assessed at 3 days, 1 month, and 3 months after initiation of treatment. They were told to report if they had symptoms of VTE or bleeding. To diagnose recurrent VTE, the same criteria used to establish the initial diagnosis had to be met in segments of deep veins or pulmonary arteries previously unaffected with thrombosis. Bleeding was defined as major if it was clinically overt and associated with a decrease in Hg of at least 2.0 g/dL, involved a need for transfusion of two or more units, or involved a critical site such as the retroperitoneum or intracranium. All outcomes were evaluated by a central adjudication committee.

▶ **Results:** In this trial, 708 patients were randomized (355 to UH; 353 to LMWH). Patients were similar at baseline. No differences were observed between the UH and LMWH groups in the rates of recurrent VTE (3.8% and 3.4%, respectively) and major bleeding in the first 10 days (1.1% and 1.4%, respectively). During 3 months of follow-up, no UH subjects with an APTT (activated partial thromboplastin time) of less than 60 seconds had recurrent VTE, vs. 3.2% of those with an APTT equal to 60 seconds; this difference was not statistically significant. No major bleeding occurred within 10 days of enrollment among patients with APTTs greater than 85 seconds or less than 85 seconds.

Testosterone Impresses In Heart Failure Trial

BY BRUCE JANCIN
Denver Bureau

BARCELONA — Modest-dose testosterone therapy brought significant functional and symptomatic improvement in men with moderate chronic heart failure in a yearlong double-blind randomized trial, Dr. Christopher J. Malkin said at the joint congress of the European Society of Cardiology and the World Heart Federation.

"This is the largest-ever prospective study of testosterone in chronic heart failure patients," said Dr. Malkin. "Testosterone is a naturally occurring and cheap hormone that seems to improve functional capacity and New York Heart Association class, compared to placebo in men with chronic heart failure. We've seen effects with achievement of levels within the normal physiologic range."

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DR. MALKIN

The clinical improvements were all the more impressive given that many patients weren't able to take the full prescribed dose of testosterone replacement therapy because of recurrent skin rashes caused by the adhesive used in the 5-mg Androderm patches. Indeed, only 42 of the original 78 participants completed the full study year for that reason.

"The testosterone increases we achieved were actually very small. We had hoped to get them up by 10 nmol/L. We achieved only about half of that," said Dr. Malkin of Royal Hallamshire Hospital, Sheffield, England.

The rationale for the clinical trial lay in the observation that heart failure (HF) entails a metabolic derangement characterized by catabolism and loss of skeletal muscle bulk due to prolonged activation of neurohormones and inflammatory cytokines.

Androgens not only play a key role in maintaining physical strength in men, they also have vasodilatory and anti-inflammatory effects highly relevant in the HF setting. Androgen levels decline with age and tend to run especially low in men with HF. In fact, at baseline, one-quarter of subjects were biochemically androgen deficient as defined by a serum testosterone below 11 nmol/L.

The men at baseline had NYHA class II or III disease with left ventricular ejection fractions of 30%-35% and moderately elevated brain natriuretic peptide levels. Few of the men were cachectic; the average body mass index was 28 kg/m^2.

The primary study end point was change in exercise capacity as measured by an incremental shuttle walk test. The walk distance improved in the testosterone group by a mean of 19% over the 180 meters at baseline, while declining in the placebo group.

At follow-up, the testosterone group also displayed significantly increased handgrip strength. Intriguingly, their mean left ventricle (LV) mass index fell by 12.7 g/m^2 and their LV cavity length increased by nearly 1 cm.

"Whether the increase in LV cavity length and decrease in LV mass are clinically relevant needs to be investigated further. It looks as if they could be emergent favorable left ventricular remodeling," Dr. Malkin said.

However, the men treated with testosterone showed no change over time in body mass index, brain natriuretic peptide levels, ejection fraction, several other echocardiographic parameters, thickness of skeletal muscle measured across the thigh, or any of the proinflammatory cytokines investigators measured.

Some men remained androgen deficient despite testosterone therapy because the dose was so small. "If we can improve their testosterone levels further we may see even better effects than in this study," the physician speculated.

Audience members congratulated Dr. Malkin for bringing scientific rigor to an area often dominated by anecdotal fountain-of-youth testimonials. But they worried about possible cardiotoxic effects of exogenous testosterone in a vulnerable HF population.

"I don't think there's any doubt that supraphysiologic levels of testosterone cause cardiotoxicity. But we're not advocating supraphysiologic levels at all. Our target was high physiologic levels—20-30 nmol/L, levels about what we'd see in elite athletes," Dr. Malkin replied.

He and his coworkers are planning a new study of testosterone therapy with or without a structured aerobic exercise program in a 2 x 2 factorial design. They'll scrap the poorly tolerated patch in favor of either a gel preparation or 3-month depot injections, which patients most prefer. ■