Heparin prophylaxis did not increase mortality and was beneficial in adults with sepsis receiving drotrecogin alfa

Levi M, Levy M, Williams MD, et al. **Prophylactic heparin in patients with severe sepsis treated with drotrecogin alfa (activated).** Am J Respir Crit Care Med. 2007;176:483-90.

Clinical impact ratings: Hospitalists ★★★★★★☆ Hematol/Thrombo ★★★★★★★ Infectious Disease ★★★★★★☆ Critical Care ★★★★★★☆

QUESTION

In adults with severe sepsis who are receiving drotrecogin alfa (activated) (DrotAA), is coadministration of heparin thromboprophylaxis equivalent to placebo?

METHODS

Design: Randomized, placebo-controlled, equivalence trial (Xigris and Prophylactic HepaRin Evaluation in Severe Sepsis [XPRESS]).
Allocation: {Concealed}†.*
Blinding: Blinded (patients, {clinicians, and outcome assessors}†).*
Follow-up period: 28 days.
Setting: 224 sites in 20 countries in North, Central, and South America; Europe; Asia; and Australia.
Patients: 1994 patients who were ≥ 18 years of age (mean age 59 y, 59% men), received treatment for severe sepsis, and had multiple organ dysfunction or a relatively high risk for death (i.e., Acute Physiology Age and Chronic Health Evaluation [APACHE] II score ≥ 25). Exclusion criteria were heparin contraindication; need for higher heparin dose than that specified in protocol or other anticoagulant medication; creatinine clearance < 30 mL/min; life expectancy < 28 days; and patient, family, or attending physician declining aggressive sepsis therapy.
Intervention: Unfractionated heparin (UFH), 5000 U subcutaneously twice daily (n = 511), low-molecular-weight heparin (LMWH) (enoxaparin), 40 mg subcutaneously once daily (n = 493), or placebo twice daily (n = 990). All patients received DrotAA at 24 μg/kg per hour for 96 hours. The first study drug injection was given as soon as possible after the DrotAA infusion was started and continued every 12 hours until the DrotAA infusion was completed.
Outcomes: All-cause mortality. Secondary outcomes included bleeding events, venous thromboembolism, and ischemic stroke.
Patient follow-up: 97% (intention-to-treat analysis).

MAIN RESULTS

At 28 days, 275 patients had died in the heparin group, and 305 had died in the placebo group. The lower limit of the 90% CI for the absolute risk difference exceeded the prespecified boundaries (Table); therefore, the criteria for equivalence were not met. The Table shows the safety results.

CONCLUSION

In adults with severe sepsis who were receiving drotrecogin alfa (activated), heparin thromboprophylaxis did not increase mortality and was safe with respect to other clinical outcomes.

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*See Glossary.

†Information provided by author.

Drotrecogin alfa (activated) (DrotAA) plus heparin vs DrotAA plus placebo in adults with severe sepsis‡

Outcomes at 28 days	DrotAA + heparin	DrotAA + placebo	Absolute risk difference (90% CI)	
Mortality§	28%	32%	–3.6% (–7.1 to –0.21)	
VTE‖	5.7%	7.0%	1.2% (–0.9% to 3.5%)	
			RRI (95% CI)	NNH
Any bleeding	12%	11%	13% (–11 to 45)	Not significant
			RRR (CI)	NNT (CI)
Serious bleeding	3.9%	5.2%	25% (–12 to 50)	Not significant
Ischemic stroke	0.5%	1.8%	71% (25 to 89)	79 (43 to 290)

‡VTE = venous thromboembolism; other abbreviations defined in Glossary. RRI, RRR, NNH, NNT, and CI calculated from data in article.
§Boundaries for equivalence in mortality were set at ± 2.8%.
‖Boundaries for equivalence in VTE were set at ± 2.5%

COMMENTARY

By examining the equivalence of thromboprophylactic heparin and placebo in adults with severe sepsis receiving DrotAA, the XPRESS trial tested a hypothesis generated by the initial DrotAA trial—Recombinant Human Protein C Worldwide Evaluation in Severe Sepsis Study (PROWESS) (1). PROWESS showed a number needed to treat of 16 to prevent 1 death at 28 days among patients with severe sepsis receiving DrotAA; however, post hoc secondary analyses suggested slightly higher mortality in patients who received heparin thromboprophylaxis (2), postulated to reflect heparin's attenuation of DrotAA's effect, increased bleeding, or another mechanism.

In a concealed allocation, blinded trial using a 1:1:2 design, XPRESS randomly assigned adults with severe sepsis receiving DrotAA to UFH, LMWH, or placebo. The primary analysis of patients receiving heparin versus placebo did not show equivalence for 28-day mortality; however, the 3.6% lower absolute risk for death in patients exposed to heparin was not significant. Bleeding and venous thrombosis rates were similar at 6 and 28 days. Patients receiving heparin had fewer ischemic strokes at 6 and 28 days.

Sepsis is a complex inflammatory state characterized by depressed endogenous anticoagulants. Heparin's antiinflammatory and anticoagulant properties may be therapeutic in sepsis, as suggested by emerging observations in humans (3).

Until the benefits of therapeutic doses of heparin are confirmed or refuted in trials, XPRESS indicates that clinicians should consider low-dose heparin thromboprophylaxis for all critically ill patients (4), regardless of DrotAA infusion, while carefully weighing risks for bleeding and thrombosis.

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References

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