Abciximab added to urokinase increased amputation-free survival in peripheral arterial occlusion of the legs

Duda SH, Tepe G, Luz O, et al. **Peripheral artery occlusion: treatment with abciximab plus urokinase versus with urokinase alone: a randomized pilot trial (the PROMPT Study).** Radiology. 2001 Dec;221:689-96.

QUESTION

In patients with peripheral arterial occlusion (PAO) of the legs, does a combination of urokinase and abciximab reduce complications and prolong amputation-free survival better than urokinase alone?

DESIGN

Randomized (allocation concealed*), blinded (patients and outcome assessors),* controlled trial with median follow-up of 5.6 to 7.0 months.

SETTING

A university-based hospital in Tübingen, Germany.

PATIENTS

70 patients who were 18 to 90 years of age (median age 68 y, 56% men) and had PAO for ≤ 6 weeks in the iliac or femoropopliteal vessels. Exclusion criteria were acute limb-threatening ischemia requiring treatment within 1 hour; recent major trauma, including resuscitation or active internal bleeding; severe hepatic or renal disorder; history of bleeding diasthesis or platelet count < 10×10^9/L; autoimmune disorders; thrombolysis within 2 weeks; contraindication to study drugs, heparin, or aspirin; or potential for pregnancy. Follow-up was complete.

INTERVENTION

Patients were allocated in a 5:2 ratio to urokinase plus abciximab (n = 50) or urokinase alone (n = 20). Urokinase was administered as an initial bolus of 25 000 IU per 10 cm of thrombus with an automated pulse-spray infusion pump and continued at 4000 IU/min for 2 hours and 2000 IU/min for another 2 hours if necessary. Abciximab was administered as a bolus injection of 0.25 mg/kg of body weight at the start of urokinase treatment and as an intravenous maintenance infusion of 0.125 µg/kg per minute for 12 hours.

MAIN OUTCOME MEASURES

The primary safety end point was rate of major complications at 30 days (procedure-related death, major bleeding, blood transfusion, or prolonged hospitalization). The primary efficacy end points were amputation-free survival and survival without open surgery or amputation at 90 days.

MAIN RESULTS

The rate of major complications at 30 days was low: Major bleeding occurred in 4 patients in the urokinase-plus-abciximab group and in no patients in the urokinase-alone group (8% vs 0%, P = 0.32). At 90 days, amputation-free survival was higher in the urokinase-plus-abciximab group than in the urokinase-alone group (P = 0.04) (Table). Survival without revascularization or amputation was also higher in the urokinase-plus-abciximab group, but the difference did not reach statistical significance (P = 0.053) (Table).

CONCLUSION

In patients with peripheral arterial occlusion of the leg, the addition of abciximab to urokinase increased amputation-free survival without increasing major bleeding complications.

Sources of funding: Centocor and Lilly Deutschland.

For correspondence: Dr. S.H. Duda, University of Tübingen, Tübingen, Germany. E-mail stephan.duda@med.uni-tuebingen.de.

*See Glossary.

Urokinase plus abciximab vs urokinase alone for peripheral arterial occlusion of the leg†

Outcomes at 90 d	Urokinase plus abciximab	Urokinase alone	RBI (95% CI)	NNT (CI)
Amputation-free survival	96%	80%	39% (1.7 to 72)	4 (2 to 76)
Survival without revascularization or amputation	90%	75%	26% (–0.5 to 50)	Not significant

†Abbreviations defined in Glossary; RBI, NNT, and CI calculated from data in article.

COMMENTARY

Acute leg ischemia is typically caused by embolic or thrombotic occlusion of either a native artery or peripheral bypass graft. Given the limb-threatening nature of the occlusion, catheter-directed thrombolysis or surgical removal of the clot is usually done emergently. The addition of a platelet glycoprotein (GP) IIb/IIIa receptor blocker to the thrombolytic regimen is well established in acute coronary syndromes but has not been rigorously studied in peripheral arterial disease. Thus, the PROMPT study provides the first randomized trial experience with the combination of agents for acute leg ischemia. The results provide evidence of efficacy for the primary end point of amputation-free survival without a significant increase in the risk for major bleeding.

Limitations of the PROMPT study include location at a single center with a relatively small sample, lack of complete blinding, and unbalanced randomization. Although the results for 1 of the primary efficacy end points were statistically significant, the estimate of the size of the effect had wide 95% confidence intervals, and a second primary end point just missed being statistically significant. Major bleeding occurred in 8% of patients receiving the GP IIb/IIIa inhibitor and in none of those receiving urokinase alone; this difference was not statistically significant, but the study lacked sufficient power to evaluate the importance of this finding. A larger, multicenter study is required to fully establish the potential safety and benefits of combining a lytic drug with a GP IIb/IIIa inhibitor in patients with acute leg ischemia.

Patients in the PROMPT study who received combined therapy had arterial patency rates and risk for reocclusion and leg hemodynamics (in those who did not have subsequent surgery) similar to patients who received lytic therapy alone. Thus, it is unclear why the combined-therapy group had better 90-day amputation-free survival. Additional studies are warranted on the combination of a GP IIb/IIIa drug with a lytic agent in acute leg ischemia.

William R. Hiatt, MD
University of Colorado Health Sciences Center
Denver, Colorado, USA