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Adjunctive Transcutaneous Ultrasound With Thrombolysis

Results of the PLUS (Perfusion by ThromboLytic and UltraSound) Trial

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Objectives We investigated whether transcutaneous ultrasound (TUS) augments coronary thrombolysis and achieves higher rates of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 and ST-segment resolution in patients with ST-segment elevation myocardial infarction (STEMI).

Background In animal coronary and peripheral artery thrombosis models, low-frequency TUS enhances and accelerates thrombolysis.

Methods In a double-blind, randomized, controlled international clinical trial, 396 patients with STEMI ≤6 h were randomized to thrombolysis alone or thrombolysis plus TUS. The 60 minute TIMI flow grade, ST-segment resolution (primary end points) and other angiographic, electrocardiographic, and clinical outcomes were compared between treatment groups.

Results The trial was halted after Safety and Efficacy Monitoring Committee interim analysis that demonstrated lack of treatment efficacy. In total, 360 patients were evaluable for angiographic, electrocardiographic, or clinical end points. Sixty minutes after thrombolytic administration, the proportion of patients achieving TIMI flow grade 3 did not differ between TUS and control groups (40.7% vs. 48.5%, respectively; $p = 0.10$). Achievement of >50% ST-segment resolution at 60 min did not differ between TUS and control groups (53.2% vs. 50.0%; $p = 0.93$). Thirty-day mortality and composite clinical events—death, reinfarction, recurrent ischemia, stroke, major bleed, left ventricular rupture (9.7 % vs. 10.2%; $p = 0.88$)—did not differ between TUS and control patients.

Conclusions Thrombolysis plus TUS failed to improve 60-min TIMI flow grade or ST-segment resolution versus thrombolysis alone. (J Am Coll Cardiol Intv 2010;3:352–9) © 2010 by the American College of Cardiology Foundation

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Currently used thrombolytic reperfusion regimens improve survival in patients with acute ST-segment elevation myocardial infarction (STEMI) (1). This clinical benefit is largely dependent on their ability to: 1) achieve timely and complete restoration of anterograde epicardial blood flow in the infarct-related artery (Thrombolysis In Myocardial Infarction [TIMI] flow grade 3) (2–4); and 2) improve microvascular or myocardial tissue level perfusion as determined by ST-segment resolution, contrast echocardiography, or TIMI perfusion grade/"blush score" (5–7). Hence, the absence of TIMI flow grade 3 and the lack of electrocardiographic ST-segment resolution after thrombolysis are strongly associated with death and poor outcome in patients with STEMI (2,3,7,8).

Approximately one-half of STEMI patients fail to achieve optimal infarct artery patency and/or myocardial tissue perfusion with current thrombolytic regimens (1–3). More aggressive antithrombotic regimens modestly increase patency rates but are associated with more bleeding and no clear mortality benefit. Therapeutic low-frequency transcutaneous ultrasound (TUS) is a potential adjunctive therapy to thrombolysis that might enhance coronary thrombolysis without increased bleeding (9). In preclinical studies, the combination of TUS and thrombolytic agents improves patency in coronary and peripheral artery thrombosis models compared with thrombolysis alone (9–15). Mechanistically, this enhanced thrombolysis effect has been attributed to TUS effects on fibrin bundle disaggregation, acoustic cavitation, microstreaming, increased clot permeability to thrombolytic agents, and coronary vasodilatation (9,16–18).

In a pilot feasibility study, we earlier tested the combination of TUS and thrombolysis in 25 STEMI patients and achieved TIMI flow grade 3 in 65% of patients at 90-min angiography (19). Therefore, we conducted the multicenter, randomized controlled PLUS (Perfusion by ThromboLytic and UltraSound) trial to investigate whether TUS could improve the proportion of STEMI patients achieving TIMI flow grade 3 and >50% ST-segment resolution 60 min after thrombolysis.

Methods

Study population. The PLUS trial was a randomized, double-blind, active-control trial conducted at 44 centers in Europe, Argentina, Canada, and the U.S. (see Online Appendix). The study was conducted according to principles of the Declaration of Helsinki and standards of the International Committee on Harmonisation Good Clinical Practice. The institutional review board at each site approved the protocol, and all patients provided written informed consent before enrollment.

Eligible patients were 18 to 75 years of age, with onset of STEMI symptoms within 6 h, ST-segment elevation ≥0.1 mV in 2 contiguous electrocardiographic (ECG) leads, and ability to provide informed consent. Exclusion criteria were pregnancy, cardiogenic shock (systolic BP <90 mm Hg), uncontrolled hypertension (>180/110 mm Hg), left bundle branch block or pacemaker ECG rhythm, prior coronary bypass surgery, percutaneous coronary intervention (PCI) within past 14 days, active internal bleeding or coagulopathy/bleeding diathesis, previous hemorrhagic stroke, or ischemic stroke within past 1 year.

Study design and randomization. Patients who met eligibility criteria were randomly assigned in a 1:1 ratio to: 1) thrombolysis plus TUS, or 2) control therapy (thrombolysis plus sham ultrasound transducer/therapy). Randomization was performed via centralized telephone hotline that assigned patients to active versus sham transducers with sealed envelopes. Trial randomization was stratified by infarct location (anterior vs. other), and randomization blocks of 6 patients were maintained at each site.

Study interventions. Aspirin (162 to 325 mg at presentation and daily) and unfractionated heparin (60 U/kg bolus) + 12 U/kg/h) or enoxaparin (30 mg IV + 1 mg/kg administered SC) were given to all patients. Open-label thrombolytic therapy, either reteplase/retavase or tenecteplase/TNKase, was administered in both treatment groups at full dose according to the manufacturer's instruction for acute STEMI. Within 5 min of thrombolytic administration, ultrasound gel and a single-use ultrasound transducer was applied to the anterior chest wall as shown in Figure 1A. The TUS patients received transcutaneous, low-frequency ultrasound therapy via the Timi3 Systems Ultrasound System (Timi3 Systems, Inc., Santa Clara, California) (Fig. 1B). This device delivered low-frequency (28.3 ± 0.3 kHz) ultrasound at maximum power (23.0 ± 0.4 W) over an effective radiating area of 57.6 ± 5.5 cm^2. Acoustic output was pulsed for 12-ms duration at a pulse repetition rate of 25 Hz yielding peak temporal average intensity of 0.12 W/cm^2 and a spatial peak pulse average intensity of 0.38 $W/cm.^2$ Control patients were attached to the same ultrasound generator plus a sham transducer and experienced mild warmth and vibration to the chest wall without therapeutic ultrasound. Ultrasound transmission was to be delivered for 60 ± 5 min unless worsening ischemia or hemodynamic compromise necessitated earlier resuscitation or angiography. Coronary angiography was mandated at 60 min after thrombolytic administration, and all subsequent revascularization decisions were left to the investigator's discretion.

Abbreviations and Acronyms

ECG = electrocardiogram
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TIMI = Thrombolysis In Myocardial Infarction
TUS = transcutaneous ultrasound

Study end points. Primary end points of the PLUS trial were the proportion of STEMI patients achieving: 1) TIMI