Tissue Plasminogen Activator in In-Hospital Cardiac Arrest with Pulseless Electrical Activity

Hannah Jordan

A. Study Purpose and Rationale

Pulseless electrical activity during cardiac arrest carries a grim prognosis; studies suggest that only four percent of patients with this rhythm survive to hospital discharge. Because a significant proportion of these patients are thought to succumb to massive pulmonary or cardiac thrombosis, thrombolytic therapy has a theoretical value in their treatment.[i] [ii] [iii] Indeed, case series and non-randomized studies have shown improved survival to hospital discharge amongst patients treated with thrombolysis in this setting[iv]. In contrast, the single randomized, controlled trial that evaluated the use of tissue plasminogen activator (t-PA) in unsuccessful resuscitations found no benefit to the intervention. This study was conducted with outpatients, and was powered to detect an absolute improvement in survival to hospital discharge of nine percent.

It is difficult to apply this information to practice during in-hospital arrests. First, inpatients are clearly a different population; many have an increased risk of deep venous thrombosis, and thus of pulmonary embolism. It is possible that massive pulmonary embolism is responsible for a greater percentage of cardiopulmonary arrests within the hospital than without. Inpatient victims of arrest may therefore stand to benefit more from thrombolytic therapy than do outpatients. Second, the only randomized, controlled study was not powered to detect an absolute improvement in survival to discharge of less than 4.8%. An improvement of even 4% would be clinically significant, and the treatment therefore deserves further evaluation.[v]

The purpose of this study is to evaluate the role of t-PA administration in inpatient victims of PEA arrest who do not respond to standard resuscitation measures.

B. Design and Statistical Analysis

a. Design

A randomized, double-blind, placebo-controlled study will be performed at six tertiary care centers on the East Coast over a five-year period.

b. Inclusion criteria

Hospitalized medical patients who suffer cardiopulmonary arrest and have or develop pulseless electrical activity which does not resolve after fifteen minutes of standard resuscitation efforts will be included. PEA will be defined as greater than twenty electrical complexes without pulse, confirmed by Doppler; the rhythm must be present for over one minute at some time during arrest and at the time of study drug administration.

c. Exclusion criteria

- Age < 18
- Asystole as initial rhythm
- DNR
- Pregnancy
- History of intracranial tumor or hemorrhage
- History of stroke/neurosurgery within < 6 wks
- End-stage liver disease
- Evidence of tamponade, electrolyte abnormality, hypo/hyperthermia, tension pneumothorax, hemorrhage, asphyxia, or airway compromise as etiology.

d. Randomization

Subjects will be randomized to receive either placebo or t-PA at the time of the onset of pulseless electrical activity. Randomization will be generated by the research pharmacy.

e. Protocol

Subjects will receive either placebo or the study drug as a bolus infusion if they have failed to respond to standard resuscitation measures (according to Advanced Cardiac Life Support protocol) after fifteen minutes and remain in PEA at the time of drug or placebo administration. Resuscitation efforts will be continued for fifteen minutes after intervention. All patients from the study group who survive to ICU admission will receive continued infusion of the study drug, as well as heparin, unless clinically contraindicated. Treatment will be unblinded at the time of admission to the ICU.

f. End Points

Admission to the Intensive Care Unit (ICU) would be the primary outcome; secondary outcomes will include survival to hospital discharge, one-year survival, neurologic outcome, and incidence of major hemorrhagic events. Neurologic outcome will be assessed using the Modified Mini-Mental State Examination, Glasgow coma Scale, Glasgow—Pittsburgh Cerebral and Overall Performance Scales, and the Functional Status Questionnaire. Standardized definitions of major and minor hemorrhage will be used.[vi] [vii]

g. Statistical Analysis

Assuming that 25 percent of victims of PEA arrest survive to ICU admission, and that an improvement to a 35 percent survival rate would be of clinical importance, this study will be designed with 80 percent power to detect an absolute increase in the rate of survival to ICU admission of ten. Calculation of the sample size, based on an alpha of five percent, shows that 588 patients would need to be enrolled. It is estimated that twenty patients will be enrolled a year at each center.

C. Data Collection

Arrest residents will complete a brief questionnaire regarding the sequence of events after the code has terminated. All survivors will be followed for the duration of their hospital stay by an on-site physician. All survivors to discharge will be followed for one year thereafter.

D. Study Procedures

a. Resuscitation

All eligible patients will have undergone standard attempts at resuscitation according to ACLS protocol at the time of the intervention. This includes prompt intubation, placement of intravenous access, and the administration of intravenous fluids and epinephrine. Prior to intervention, the following will be done:

- Bilateral breath sounds will be confirmed
- Most recent laboratory values will be analyzed by the code director
- Chart will be checked for a DNR order
- Normal saline will be hung; a minimum of 250 cc will be infused
- Most recent progress note will be checked to r/o exclusion criteria

b. Study drug

Tissue plasminogen activator will be administered to the study group as a 15-mg bolus followed by a 30-minute infusion of 50 mg, then a 60-minute infusion of 35 mg, a regimen used in recanalization following myodardial infarction. Higher boluses (50 mg over 2 minutes followed by 50 mg over 30 minutes) have been given in positive studies of t-PA in the arrest setting; however, this dose has not been sufficiently studied to estimate a rate of expected hemorrhage.[viii]

c. Placebo

Placebo, to be prepared by a blinded pharmacist, will be indistinguishable from the study drug, and will be infused in the same fashion.

d. Adverse Effects

The main adverse effect of concern is major hemorrhage; please see details below. Previous studies have found that the potential benefits of thrombolysis outweigh the possible risk associated with use of the medication in this clinical situation. [ix]

e. Subsequent Medical Treatment

All patients who survive to ICU admission would be monitored according to standard ICU protocol. Patients from the study group will receive the remainder of the t-PA infusion and heparin, as detailed above.

f. Study Duration

Assuming that approximately twenty patients would be enrolled at each institution a year, the study would be performed over five years.

Please see attached flow sheet.

E. Study Drug

a. Description and Rationale

Tissue Plasminogen Activator (t-PA) is approved for use in the emergent treatment of pulmonary and cardiac thrombosis. It will be used based on its efficacy and relative safety as shown in previous clinical trials. [x xi xii]

b. Dosage

Please see "Study Drug"

c. Preparation

The study drug or placebo will be provided from the research pharmacy to the general pharmacy. An on-call pharmacist will carry a pager which will be activated by the code leader at the time of the identification of PEA. The study drug or placebo will then be prepared by the pharmacist, who will be blinded to the contents of the preparation. The vials will be rushed to the arrest scene by the pharmacist. It is estimated that the study treatment will arrive at the scene of arrest approximately fifteen minutes after the pharmacist is paged.

d. Side Effects

The expected rate of hemorrhage associated with t-PA administration in the setting of acute myocardial infarction is 8.5 percent overall and 0.5 percent major hemorrhage.[xiii]

F. Medical Device

N/A

G. Questionnaires

A brief questionnaire will be filled out by the arrest resident after each arrest studied.

H. Study Subjects

a. Inclusion/Exclusion Criteria

Please see Design and Statistics section.

b. Consent

An exemption from informed consent requirements will be requested according to emergency research regulations as stipulated in the IRB's Standard Operating Procedures and Code of Federal Regulations.[xiv, xv] Exemption will be applied for on the basis that:

1. Subjects will be unable to give consent because of their medical condition
2. The study intervention must be made as rapidly as possible in order to provide a benefit
3. There is no reasonable way to identify prospective participants in advance
4. Subjects will be facing a life-or-death situation that necessitates intervention

5. Previous studies indicate a possible benefit to the individual subject
6. Risks associated with the intervention are reasonable in light of the potential benefits and poor prognosis without treatment
7. The study is necessary to improve success in treatment of PEA

The following will be provided as additional protections:

1. Plans for the study as well as risks and benefits will be publicized within the community to the best of the investigator's ability.
2. An independent data monitoring committee will exercise oversight of the investigation.
3. All survivors, or family members or legal representatives of deceased participants, will be notified of the study proceedings after intervention
4. A new drug exemption will be obtained for the t-PA if deemed necessary by the IRB.

I. Recruitment

N/A

J. Confidentiality

A unique study number will be assigned to each subject to record data pertaining to that individual. All information obtained for the study will be strictly confidential and kept in a secure location, accessible only to investigators.

K. Potential Conflict of Interest

All potential proprietary interest in the study medication will be fully disclosed.

L. Location

Six tertiary care centers in the north-eastern United States.

M. Potential Risks

Please see section C for adverse drug effects.

N. Potential Benefits

Thrombolysis can be life-saving in the treatment of pulmonary and coronary thrombosis. Refining the application of this treatment has the potential to improve outcomes amongst a group of patients that is rarely studied.

O. Alternatives

no treatment

P. Compensation

none

Q. Costs

none

R. References

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9. Ibid.

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11. Bottiger B et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful resuscitation: a prospective clinical trial. The Lancet 2001; 357: 1583—85.

12. Micromedex overview of Alteplase, quoting rates from the GUSTO trial.

13. Ibid.

14. Exception from informed consent requirements for emergency research, Code of Federal Regulations, 50.24, 1996

15. Emergency research consent waiver, Standard Operating Procedures of the Columbia Presbyterian Institutional Review Board, 2003

Additional References

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