Resuscitation (2006) **69**, 399—406

ELSEVIER

RESUSCITATION

www.elsevier.com/locate/resuscitation

CLINICAL PAPER

Empiric tenecteplase is associated with increased return of spontaneous circulation and short term survival in cardiac arrest patients unresponsive to standard interventions☆

William P. Bozeman[a,*], **Douglas M. Kleiner**[b], **Kevin L. Ferguson**[c]

[a] *Department of Emergency Medicine, Wake Forest University, Medical Center Blvd., Winston-Salem, NC 27157, USA*
[b] *Department of Emergency Medicine, University of Florida, Jacksonville, FL, USA*
[c] *Department of Emergency Medicine, University of Florida, Gainesville, FL, USA*

Received 17 August 2005; received in revised form 28 September 2005; accepted 28 September 2005

KEYWORDS
Cardiac arrest;
Resuscitation;
Thrombolysis

Summary
Background: Prospective and retrospective studies have shown that empiric use of fibrinolytic agents in sudden cardiac arrest is safe and may improve outcomes in sudden cardiac arrest. Use of fibrinolytic agents for this indication is increasing in response to these data.
Methods: A prospective multicenter observational trial was performed in three emergency departments (EDs) to determine the proportion of patients that respond to empiric fibrinolysis with tenecteplase (TNK) after failing to respond to Advanced Cardiac Life Support (ACLS) measures. Cardiac arrest patients unresponsive to ACLS, who were given TNK by their treating physician, were enrolled in an outcome registry. Return of spontaneous circulation (ROSC), survival, complications, and neurological outcomes were recorded.
Results: Fifty patients received TNK after a mean of 30 min of cardiac arrest and eight doses of ACLS medications. One hundred and thirteen concurrent control patients received standard ACLS measures. ROSC occurred in 26% of TNK patients (95% confidence interval (CI) 16—40%) compared to 12.4% (95% CI 6.9—20%) among ACLS controls ($p = .04$); 12% (4.5—24%) of TNK patients survived to admission compared to none in the control group ($p = .0007$); 4% (0.5—14%) survived to 24 h (p = NS); and 4% (0.5—14%) survived to hospital discharge (p = NS). All survivors had a good neurological outcome (Cerebral Performance Category (CPC) 1—2). One intracranial hemorrhage (ICH) occurred. No other significant bleeding complications were observed.

☆ A Spanish translated version of the summary of this article appears as Appendix in the online version at 10.1016/j.resuscitation.2005.09.027.

* Corresponding author. Tel.: +1 336 716 1740; fax: +1 336 716 1705.
E-mail address: wbozeman@wfubmc.edu (W.P. Bozeman).

0300-9572/$ — see front matter
doi:10.1016/j.resuscitation.2005.09.027

Conclusions: Empiric fibrinolysis with TNK in cardiac arrest is associated with increased ROSC and short term survival, and with survival to hospital discharge with good neurological function in patients who fail to respond to ACLS. Results may improve with earlier administration. Prospective controlled interventional trials are indicated to evaluate this promising new therapy.

Introduction

Sudden unexpected cardiac arrest is the most common cause of adult death. It is estimated to occur from 250,000 to 480,000 times yearly in the United States and is frequently the first and only manifestation of coronary artery disease (CAD).[1–4] Standard prehospital and emergency treatment using Advanced Cardiac Life Support (ACLS) measures have produced disappointing results, with overall survival rates ranging from 5 to 10%.[5–7]

Epidemiological studies suggest that coronary artery disease is the most common cause of sudden cardiac arrest, producing arrest within an hour of symptom onset by massive myocardial infarction (MI) or ischemia-related dysrhythmia in 56—88% of cases.[2,3,8,9] Pulmonary embolism is the next most common cause, estimated to produce 4.8—9.6% of cases.[10–13] The remainder of cases may be produced by intracranial hemorrhage (ICH), aortic dissection or aneurysmal rupture, and a variety of other causes.[10]

Systemic fibrinolysis is used in the treatment of patients suffering from acute MI and pulmonary embolism producing hemodynamic instability, thus fibrinolytic agents may be indicated in the large majority of sudden cardiac arrest patients. These agents have been avoided previously in the cardiac arrest setting due to concerns of potential bleeding complications produced by the trauma of chest compressions during cardiopulmonary resuscitation (CPR). However, several studies conducted in the early 1990s suggest that bleeding complications are not increased after fibrinolysis in combination with CPR.[14–19] In response to these data, case reports, retrospective studies, and prospective studies have begun to appear, suggesting that systemic fibrinolysis combined with CPR may improve both overall survival and neurological outcomes markedly.[20–25]

Recognizing that the current literature on empiric fibrinolysis as a treatment for sudden cardiac arrest suggests a lack of harm and potentially large increases in survival, many clinicians consider empiric fibrinolytic agents in selected cases of cardiac arrest. Tenecteplase (TNK), an FDA approved fibrinolytic agent given as a single bolus injection, is attractive for use in the resuscitation setting because of its ease of administration, pharmacokinetic profile, and fibrin specificity resulting in a low incidence of bleeding.[26] We performed a prospective multicenter non-randomized observational trial to record whether patients in cardiac arrest who do not respond to ACLS interventions may respond to empiric fibrinolysis with TNK.

Materials and methods

With approval from the institutional review board, a prospective multicenter observational outcomes registry was established. Surveillance of cardiac arrest treatment was established from January through September 2003 at three emergency departments (EDs) in two neighboring cities with a combined annual patient volume of approximately 130,000. These included one urban teaching hospital (ED volume 75,000 k/year), one suburban/rural teaching hospital (ED volume 38,000 k/year), and one urban non-teaching hospital (ED volume 17,000 k/year).

Patients who received empiric TNK for the treatment of non-traumatic cardiac arrest refractory to standard ACLS measures qualified for enrollment in the outcomes registry. The decision to administer fibrinolysis was made on a case-by-case basis by the treating attending physician, and standard weight based doses were used. Informed consent for further outcome recording was obtained from family members of patients who survived to hospital admission.

Demographic and clinical information were collected immediately for study patients by on call research assistants using prehospital and ED treatment records and personal interviews with treating physicians and nurses. Defining the actual time of onset of cardiac arrest is problematic in prehospital resuscitation studies; therefore, resuscitation time was measured from the first confirmation of cardiac arrest and initiation of CPR by any health care provider (EMS provider, nurse, or physician) until termination of efforts or sustained ROSC. In addition, the total number of ACLS medication doses

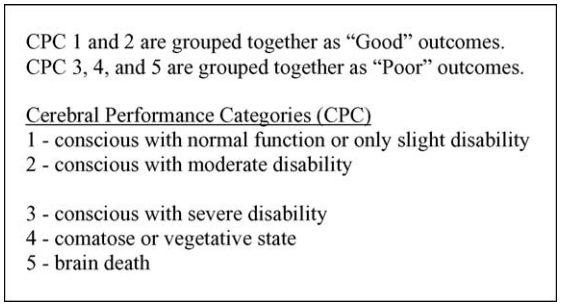

Figure 1 The Glasgow—Pittsburgh Cerebral Performance Categories.

was recorded. This measure included only medications directed toward restoration of a perfusing rhythm in pulseless patients, such as epinephrine (adrenaline), atropine, lidocaine, amiodarone, etc. It did not include medications that are recommended in the ACLS guidelines for non-arrest situations such as diuretics, pressors, sedatives, and paralytic agents. Cumulative epinephrine doses and number of defibrillations were also recorded.

A concurrent control group of non-traumatic cardiac arrest patients at the same three institutions who did not respond to standard ACLS and did not receive fibrinolysis was also recorded. Demographic and case data for these patients were determined by chart review at the conclusion of the study.

Primary outcome measures included return of spontaneous circulation (ROSC), survival to ICU admission, survival at 24 h, and survival to hospital discharge. Bleeding complications and transfusion requirements were recorded. Neurological outcome among survivors were determined by Glasgow—Pittsburgh Outcome Categories.[27] This scale results in Cerebral Performance Categories (CPC) of 1—5, with CPC 1 and 2 grouped as ''good'' neurological outcome and CPC 3, 4, and 5 grouped as ''poor'' neurological outcome (Figure 1).

Data were entered into a computerized spreadsheet (Excel, Microsoft Corp., Redmond, WA) and descriptive analysis was performed. Statistical analysis included confidence interval (CI) determination and comparisons of groups by Fisher's exact test using commercial statistical software (InStat 3.06, GraphPad Software Inc., San Diego, CA).

Results

During the study period, 50 patients who did not respond to standard ACLS measures received empiric fibrinolysis with TNK in the ED. An additional 113 patients received standard ACLS measures without fibrinolysis and were declared dead in the Emergency Department. An Utstein-style analysis diagram is shown (Figure 2). Patients in each group had similar sex distributions and comorbidities (Table 1). Patients who received fibrinolysis tended to be younger, more likely to have had a witnessed arrest, and have shorter prehospital CPR times. Total CPR times were similar, but patients who received TNK had longer ED CPR times and received more doses of ACLS medication and epinephrine than the ACLS-only controls.

Among the 50 patients who received TNK, the mean age was 58 years (range 27—95 years), and 56% were male. Arrest occurred in the prehospital setting in 80% and in the ED in 20%. TNK was administered after a mean of 30 min of CPR (range 7—74) and a mean of 8 (range 4—15) administrations of ACLS medications. Cardiac rhythms at the time of fibrinolysis are shown in Table 2. Doses of TNK ranged from 30 to 50 mg, with a mean of 0.54 mg/kg (range 0.26—0.77 mg/kg).

ROSC occurred after empiric TNK in 26% (13 of 50 patients) (95% CI 16—40%) versus 12.4% (14 of 113 patients) in the standard ACLS control group (95% CI 6.9—20.0%) ($p = .04$). The patients who responded with ROSC after TNK had a mean age of 58 years (range 27—95 years). Initial cardiac arrest occurred in the prehospital setting in 77% and in the ED in 23%. Responders received TNK after a mean of 28 min of CPR (range 5—74 min) and seven doses of ACLS medications (range 4—12 doses). ROSC occurred in a mean of 7 min after giving of TNK (range 3—12 min) and was seen in patients with ventricular fibrillation, PEA, and asystole at the time of fibrinolysis (Table 2).

Survival to ICU admission occurred in 12% (6 of 50) TNK patients (95% CI 4.5—24.3%) versus none in the control group ($p = .0007$). Survival at 24 h was seen in 4% (2 of 50) TNK patients (95% CI 0.5—13.7%) (p = NS versus controls), and survival to hospital discharge occurred in 4% (2 of 50) TNK patients (95% CI 0.5—13.7%) (p = NS versus controls; Figure 2). All survivors had a good neurological outcome (CPC 2) (Figure 3).

Complications among the 50 TNK patients included one subarachnoid hemorrhage (2%) in a patient who died after ICU admission, and two episodes of blood tinged gastric aspirate noted after placement of a nasogastric tube. No other bleeding complications were observed and no blood transfusions were required.

One survivor, a 53-year-old male without known medical problems, had a suspected primary dysrrhythmic cardiac arrest in the prehospital setting after using cocaine. He had received an estimated 32 min of CPR and seven doses of ACLS medications

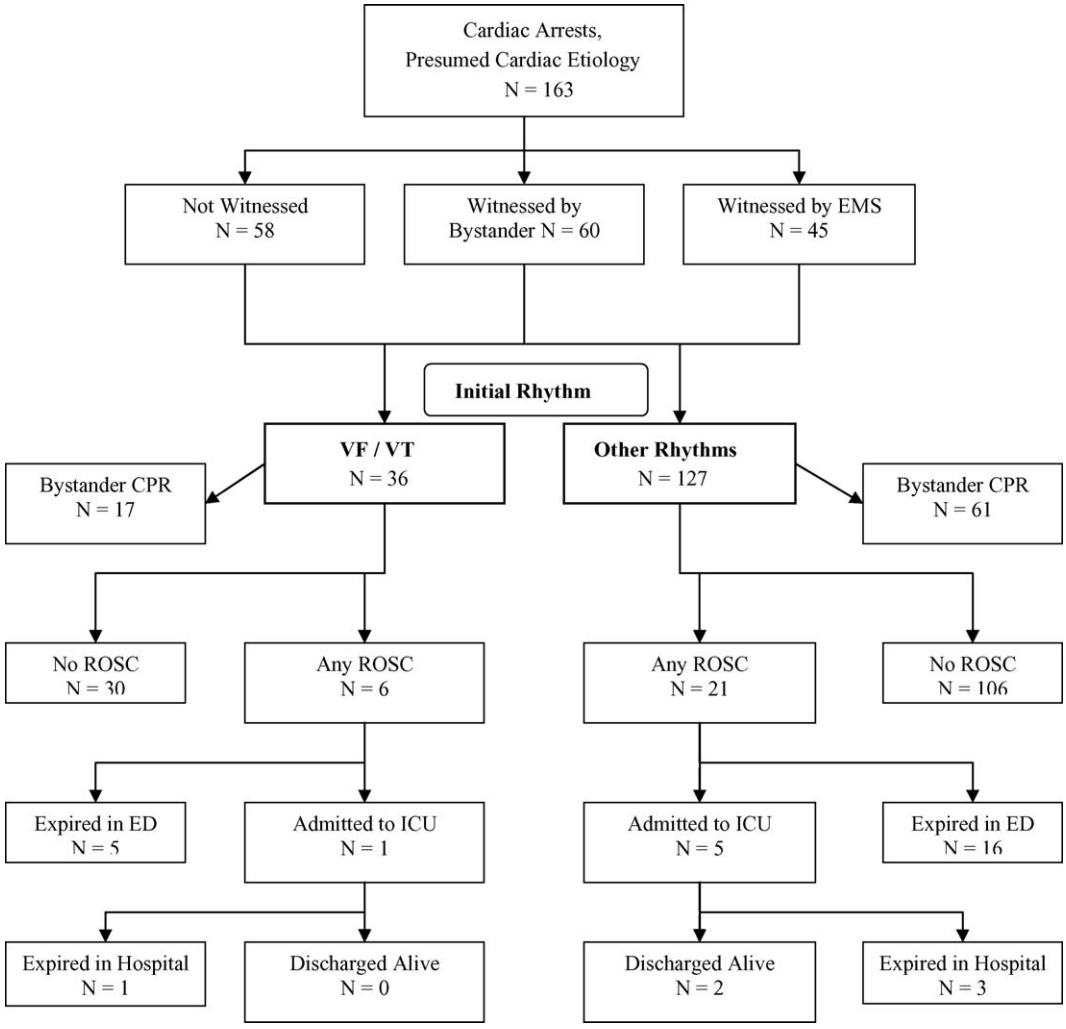

Figure 2 Utstein-style cardiac arrest group summary.

(three epinephrine, three atropine, and one sodium bicarbonate) and was asystolic at the time of giving TNK. He had ROSC 4 min later and stabilized. Subsequent serial cardiac enzyme measurements were normal and he had an unremarkable echocardiogram while in hospital. Cardiac catheterization was not performed. He was alert, conversant and ambulatory at discharge (CPC 1—2), with some difficulty with concentration and phonation. The other survivor, a 71-year-old male, had multiple medical problems including chronic obstructive pulmonary disease, hypertension, congestive heart failure, renal insufficiency, and Alzheimer's disease. He was transported via EMS from a nursing facility for chest discomfort and difficulty breathing. He suffered a witnessed cardiac arrest shortly after arrival in the emergency department. He received 11 min of CPR and nine doses of ACLS medications (four epinephrine, three atropine, one sodium bicarbonate, and one calcium chloride) and was in PEA at the time of TNK administration. He had ROSC and stabilized 6 min later. His post-arrest EKG was non-diagnostic. Subsequent cardiac enzymes showed a peak Troponin T of 0.124. An echocardiogram revealed normal left ventricular size and function, without wall motion abnormalities. Cardiac catheterization was not performed. He recovered to a conscious and communicative mental status with moderate disability (CPC 2), approximately his baseline status, and was discharged to a nursing facility.

Discussion

This prospective multicenter observational study of empiric fibrinolysis with tenecteplase in sudden cardiac arrest is, to the authors' knowledge, the first in the United States. Similar to the European experience with tissue plasminogen activator (TPA),

Table 1 Patient and resuscitation characteristics

	TNK ($n = 50$)	Controls ($n = 113$)
Demographics		
Age (years)	58 (53—63) [Range 27—95, median 59]	65 (62—68) [Range 23—95, median 65]
Sex (%)		
Male	56 (41—70)	55 (45—64)
Female	44 (30—59)	45 (36—55)
Race (%)		
African American	68 (53—81)	56 (46—65)
Caucasian	32 (20—47)	43 (34—53)
Other/unavailable	—	1 (0—5)
Medical history (%)		
Unknown	20 (10—34)	14 (8—22)
Hypertension	32 (20—47)	46 (37—56)
Coronary artery disease	24 (13—38)	19 (12—27)
COPD/asthma	18 (9—31)	16 (10—24)
Diabetes	14 (6—27)	20 (13—29)
Congestive heart failure	12 (5—24)	15 (9—23)
Stroke	6 (1—17)	9 (4—16)
Cancer	6 (1—17)	11 (6—18)
Venous thromboembolic disease	4 (0—14)	—
Hypercholesterolemia	2 (0—11)	5 (2—11)
Resuscitation profile		
Arrest location (%)		
Out of hospital	80 (66—90)	68 (59—77)
Emergency department	20 (10—34)	32 (23—41)
Witnessed arrest* (%)		
	82 (69—91)	54 (44—63)
Bystander CPR	46 (32—61)	49 (39—58)
Initial cardiac rhythm (%)		
Ventricular fibrillation	28 (16—42)	20 (13—29)
Pulseless electrical activity	32 (20—47)	38 (29—48)
Asystole	40 (26—55)	39 (30—49)
Unavailable	—	3 (1—8)
	Mean	Mean
CPR times (min)		
Prehospital*	22 (18—26)	30 (27—34)
Emergency department*	26 (23—30)	16 (13—18)
Total	43 (39—47)	36 (33—39)
ACLS medications (number of doses)		
Prehospital	4.3 (3.4—5.2)	5.6 (4.9—6.3)
Emergency department*	6.7 (5.7—7.7)	4.6 (4.0—5.3)
Total*	10.0 (9.3—10.6)	8.4 (7.8—9.1)
Cumulative epinephrine dose (mg)*	6.0 (5.0—7.0)	4.4 (4.0—4.8)
Defibrillated (%)	64 (49—77) [Range 1—14, median 4x]	47 (37—56) [Range 1—13, median 3x]

Observed percentages and mean values. (95% confidence intervals in parentheses.) Non-overlapping confidence intervals are marked with an asterisk (*).

these results suggest improvement in cardiac arrest outcomes. Even though the administration of fibrinolysis was delayed for a mean of 30 min after cardiac arrest, ROSC occurred in approximately one quarter of patients. There was an increase in short term survival to hospital admission compared to standard ACLS, and a 4% survival to discharge with good neurological outcome was seen.

Table 2 Cardiac rhythms at time of fibrinolysis

Rhythm	All TNK patients	Responders*
VF	7	2
PEA	22	5
Asystole	21	6
Total	50	13

VF: ventricular fibrillation; PEA: pulseless electrical activity.
* Responders: patients with return of spontaneous circulation after fibrinolysis.

Proposed mechanisms of action of fibrinolytics during cardiac arrest include direct lysis of coronary and pulmonary thrombi, as well as systemic microfibrinolysis. The most intuitive mechanism is direct thrombolysis at the site of coronary or pulmonary artery occlusion. Resolution of obstructing thrombi in coronary or pulmonary vessels may result in ROSC and hemodynamic stabilization. Interestingly our data show a mean time from fibrinolytic administration to ROSC of just 7 min among responders. This time interval may be too short to accomplish complete lysis of large thrombi at occluded vessels, suggesting that partial resolution of flow past an occluded vessel may result in ROSC or that other effects such as systemic microfibrinolysis may also be important in achieving ROSC.

Animal and human trials have indicated that a generalized hypercoagulable state occurs during cardiac arrest with CPR.[28–31] This is thought to result in microcirculatory fibrin formation. By relieving these micro-occlusive thrombi at the capillary bed level, systemic fibrinolysis may improve delivery of oxygen, glucose, and antiarrhythmic medications to cardiac and other tissues and improve the removal of metabolic by-products. This collective action may promote ROSC by termination of cardiac dysrhythmias and may mitigate reperfusion disorders.

Fibrinolytic agents may positively affect neurological recovery after cardiac arrest by similar microcirculatory action in the central nervous system. Micro-occlusive thrombi in cerebral vessels may prevent cerebral tissue perfusion even after systemic ROSC, producing the post-cardiac arrest cerebral no-reflow phenomenon. Animal studies of this phenomenon suggest that fibrinolysis given during cardiac arrest significantly reduces cerebral no-reflow after cardiac arrest.[32] Human reports include a number of neurologically intact survivors after prolonged CPR and show improved neurological outcome in a series of cardiac arrest patients treated with fibrinolytics.[20,24,25]

This observational trial also demonstrates clinician choice of tenecteplase as a rescue agent in the treatment of cardiac arrest. The ability to give full dose systemic fibrinolysis with a single bolus injection makes TNK attractive in the resuscitation setting. Other available agents such as alteplase and reteplase require infusion over minutes to hours or multiple injections to achieve full dose fibrinolysis. In addition, the fibrin specificity of tenecteplase has resulted in fewer bleeding complications compared

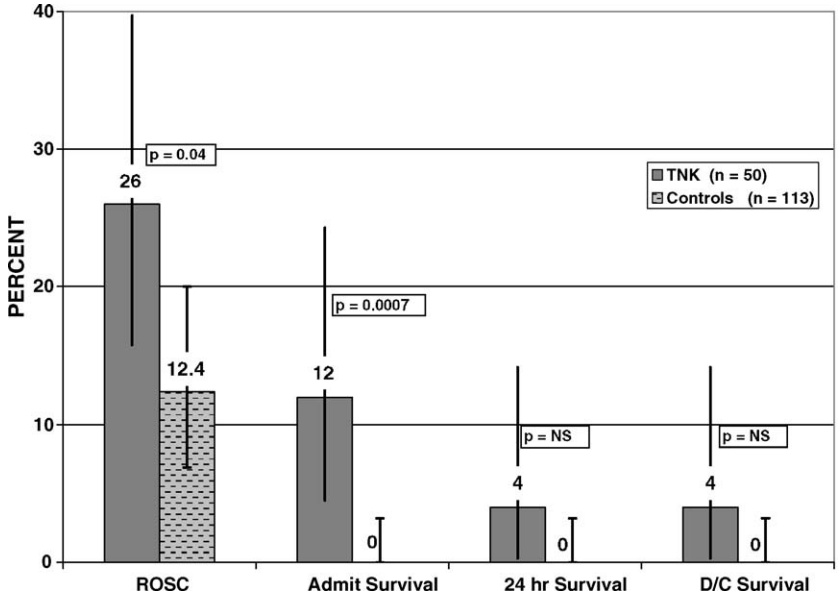

Figure 3 Clinical response to empirical TNK fibrinolysis during cardiac arrest. (Bars indicate 95% confidence intervals, *p*-values vs. ACLS-only control group.)

to alteplase in the setting of ST segment elevation myocardial infarction.[26] This may also hold true in the cardiac arrest setting. A recent small study has demonstrated the feasibility of using TNK as a resuscitation agent and confirms a significantly increased rate of ROSC in cardiac arrest patients treated with TNK.[33]

Complications in this series included a single case of subarachnoid intracranial hemorrhage in a patient who received TNK during cardiac arrest, had return of spontaneous circulation, was admitted to the intensive care unit, and later died. It could not be determined whether the ICH was present prior to fibrinolysis. However, an ICH rate of 2% is consistent with the complication rate of systemic fibrinolysis for ST elevation myocardial infarction (without CPR) and with the European experience with empiric fibrinolysis during cardiac arrest.[23] Two patients had blood noted after nasogastric tubes were placed after fibrinolysis and ROSC. No interventions were needed. No other bleeding complications were observed, and no blood transfusions were required.

Having recognized a trend toward use of rescue fibrinolysis in cardiac arrest patients by clinicians in the region by anecdotal reports, the authors designed and conducted this trial as an observational case series to record outcomes. Fibrinolytics were not given as part of an interventional study protocol. Rather, they were used at the discretion of the treating physician. They were generally used as agents of last resort after standard ACLS interventions were judged to be ineffective. In general, patients with a history suggestive of collapse due to a cardiac or pulmonary embolic etiology were considered potential candidates for fibrinolysis by the treating physicians, while patients with a history suggestive of intracranial hemorrhage, occult bleeding, or aortic dissection/aneurysmal rupture leading to cardiac arrest were not. Pre-study information sessions and signs providing study information and contact numbers all emphasized that the decision to use fibrinolytic agents was purely a clinical decision left to the treating physician.

Limitations of this study include the observational study design. Physicians used unstructured clinical judgment when deciding whether to administer TNK to their patients. This presents a high risk of selection bias. Not surprisingly, younger healthier patients with witnessed cardiac arrests and shorter prehospital times tended to be selected for TNK administration. Other unmeasured variables that impacted the treating physician's assessment of a patient's potential for recovery undoubtedly also came into play in the decision to use fibrinolysis. ED resuscitation efforts continued somewhat longer in the TNK group, and a correspondingly larger number of medications were used (Table 1). A randomized controlled trial design is needed to address these limitations.

Other limitations include a small study size, cardiac arrest interventions that were guided by the ACLS protocols but not standardized, and the variable timing of TNK. Further, heparin was not used in any cases until after ROSC. The contribution of heparin in this setting is unknown but may be important.[34] The mean time of 30 min from arrest to fibrinolysis represents a long interval for any cardiac arrest intervention. Future studies should seek to reduce this interval while still allowing for possible response to standard ACLS interventions by conducting interventions in the prehospital setting as well as in the ED. Patients who were declared dead after ACLS efforts by EMS in the field were not included, and the total number of cardiac arrests (those transported to other hospital facilities by the several EMS providers) in the region during the study period is unknown. Lastly, the full details of patients' medical histories and pre-arrest events were frequently unknown at the time of treatment.

Conclusion

In summary, this prospective observational trial found that empiric fibrinolysis with TNK during cardiac arrest unresponsive to standard ACLS measures is associated with an increased rate of ROSC, increased short term survival, and neurologically intact survival to hospital discharge. This is in concordance with several previous investigations utilizing systemic fibrinolysis in cardiac arrest. Combined with animal and human evidence of improved neurological outcome after cardiac arrest, these data support the use of empiric fibrinolysis in selected cases of cardiac arrest refractory to standard ACLS measures and further reinforce the need for prospective randomized controlled trials of this therapy. Such trials will require adequate power to demonstrate differences in clinically relevant outcome and complications; will necessarily use an exemption from informed consent; and should institute fibrinolysis as soon as feasible in both the prehospital and emergency department settings.

Conflict of interest statement

None of the authors report any financial or personal conflicts of interest.

Acknowledgements

The authors gratefully acknowledge the support and assistance of Dia Dooley, CTC, and Drs. Aaron McKinney, Kevin King, and Lilane Rifenberg in the conduct of this investigation. A grant from the Investigator Sponsored Trial Program of Genentech, Inc. ($40,500) supported the administrative costs of the trial. No study medications were provided. Genentech had no input or control over the design or conduct of the trial, or in the development of the manuscript.

References

1. Zheng ZJ, et al. Sudden cardiac death in the United States, 1989 to 1998. Circulation 2001;104(18):2158—63.
2. Zipes DP, Wellens HJ. Sudden cardiac death. Circulation 1998;98(21):2334—51.
3. Engelstein E, Zipes DP. Sudden cardiac death. In: Alexander R, Schlant R, Fuster V, editors. Hurst's The Heart Arteries and Veins, vol. 1. McGraw Hill Health Professions Division; 1998. p. 1081—112.
4. Escobedo LG, Zack MM. Comparison of sudden and non-sudden coronary deaths in the United States. Circulation 1996;93(11):2033—6.
5. Stiell IG, et al. Advanced cardiac life support in out-of-hospital cardiac arrest. N Engl J Med 2004;351(7):647—56.
6. Nichol G, et al. Effectiveness of emergency medical services for victims of out-of-hospital cardiac arrest: a metaanalysis. Ann Emerg Med 1996;27(6):700—10.
7. Callaway CW. Improving neurologic outcomes after out-of-hospital cardiac arrest. Prehosp Emerg Care 1997;1(1):45—57.
8. Spaulding CM, et al. Immediate coronary angiography in survivors of out-of-hospital cardiac arrest. N Engl J Med 1997;336(23):1629—33.
9. Engdahl J, et al. The epidemiology of out-of-hospital 'sudden' cardiac arrest. Resuscitation 2002;52(3):235—45.
10. Courtney DM, et al. Pulseless electrical activity with witnessed arrest as a predictor of sudden death from massive pulmonary embolism in outpatients. Resuscitation 2001;49(3):265—72.
11. Gallerani M, et al. Sudden death from pulmonary thromboembolism: chronobiological aspects. Eur Heart J 1992;13(5):661—5.
12. Manfredini R, et al. Out-of-hospital sudden death referring to an emergency department. J Clin Epidemiol 1996;49(8):865—8.
13. Kurkciyan I, et al. Pulmonary embolism as a cause of cardiac arrest: presentation and outcome. Arch Intern Med 2000;160(10):1529—35.
14. Cross SJ, et al. Safety of thrombolysis in association with cardiopulmonary resuscitation. BMJ 1991;303(6812): 1242.
15. Tenaglia AN, et al. Thrombolytic therapy in patients requiring cardiopulmonary resuscitation. Am J Cardiol 1991;68(10):1015—9.
16. Scholz KH, et al. Frequency of complications of cardiopulmonary resuscitation after thrombolysis during acute myocardial infarction. Am J Cardiol 1992;69(8):724—8.
17. van Campen LC, van Leeuwen GR, Verheugt FW. Safety and efficacy of thrombolysis for acute myocardial infarction in patients with prolonged out-of-hospital cardiopulmonary resuscitation. Am J Cardiol 1994;73(13):953—5.
18. Spohr F, Bottiger BW. Safety of thrombolysis during cardiopulmonary resuscitation. Drug Saf 2003;26(6):367—79.
19. Kurkciyan I, et al. Major bleeding complications after cardiopulmonary resuscitation: impact of thrombolytic treatment. J Intern Med 2003;253(2):128—35.
20. Newman DH, Greenwald I, Callaway CW. Cardiac arrest and the role of thrombolytic agents. Ann Emerg Med 2000;35(5):472—80.
21. Ruiz-Bailen M, et al. Efficacy of thrombolysis in patients with acute myocardial infarction requiring cardiopulmonary resuscitation. Intensive Care Med 2001;27(6):1050—7.
22. Bottiger BW, et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. Lancet 2001;357(9268):1583—5.
23. Lederer W, et al. Recombinant tissue plasminogen activator during cardiopulmonary resuscitation in 108 patients with out-of-hospital cardiac arrest. Resuscitation 2001;50(1):71—6.
24. Schreiber W, et al. Thrombolytic therapy after cardiac arrest and its effect on neurological outcome. Resuscitation 2002;52(1):63—9.
25. Lederer W, et al. Long-term survival and neurological outcome of patients who received recombinant tissue plasminogen activator during out-of-hospital cardiac arrest. Resuscitation 2004;61(2):123—9.
26. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Assessment of the safety and efficacy of a new thrombolytic investigators. Lancet 1999;354(9180): 716—22.
27. Cummins RO, et al. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the Utstein style. A statement for health professionals from a task force of the American Heart Association, the European Resuscitation Council, the Heart and Stroke Foundation of Canada, and the Australian Resuscitation Council. Circulation 1991;84(2):960—75.
28. Bottiger BW, et al. Activation of blood coagulation after cardiac arrest is not balanced adequately by activation of endogenous fibrinolysis. Circulation 1995;92(9):2572—8.
29. Johansson J, et al. Antithrombin reduction after experimental cardiopulmonary resuscitation. Resuscitation 2003;59(2):235—42.
30. Gando S, et al. Massive fibrin formation with consecutive impairment of fibrinolysis in patients with out-of-hospital cardiac arrest. Thromb Haemost 1997;77(2):278—82.
31. Bottiger BW, et al. Marked activation of complement and leukocytes and an increase in the concentrations of soluble endothelial adhesion molecules during cardiopulmonary resuscitation and early reperfusion after cardiac arrest in humans. Crit Care Med 2002;30(11):2473—80.
32. Fischer M, et al. Thrombolysis using plasminogen activator and heparin reduces cerebral no-reflow after resuscitation from cardiac arrest: an experimental study in the cat. Intensive Care Med 1996;22(11):1214—23.
33. Fatovich DM, Dobb GJ, Clugston RA. A pilot randomised trial of thrombolysis in cardiac arrest (the TICA trial). Resuscitation 2004;61(3):309—13.
34. Bottiger BW, Padosch SA, Wenzel V. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. N Engl J Med 2002;347(16):1281—2, author reply 1281—2.