Tissue Plasminogen Activator in Out-of-Hospital Cardiac Arrest with Asystole

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Citation

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Abstract

This study was conducted to determine whether administration of recombinant tissue plasminogen activator in out-of-hospital cardiac arrest with asystole as the initial rhythm improves post-resuscitation outcome. A retrospective chart review of 177 patients with out-of-hospital cardiac arrest who underwent attempted resuscitation by the emergency medical service was performed for a six-year observation period. A total of 34 patients received thrombolytic therapy during resuscitation and were compared to 102 controls, closely matched according to arrival status. Administration of thrombolytics was optional. Return of spontaneous circulation occurred in 23 patients in the treatment group (68% vs. 33% in controls; p=0.001). Ten patients survived the first 24 hours (29% vs. 14% in controls; p=0.038), while four survived more than ten days (12% vs. 5% in controls; p=0.163). Three patients from the treatment group were ultimately discharged from hospital (9% vs. 3% in controls; p=0.570). Generally, the outcome of patients with asystole as the initial rhythm in cardiac arrest is poor. Thrombolytic therapy, however, may substantially improve frequency of return of spontaneous circulation and increase 24-hour survival in patients with asystole in out-of hospital cardiac arrest.

INTRODUCTION

The survival rate for patients with out-of-hospital cardiac arrest (OHCA) is generally regarded to be very poor for patients with asystole as the initial rhythm [1,2]. Thrombolytic therapy during cardiopulmonary resuscitation (CPR) was reported to improve survival and stabilize patients with pulmonary embolism and myocardial infarction [3, 4]. Furthermore, thrombolysis after OHCA has beneficial effects on cerebral reperfusion and is associated with improved cerebral outcome [5, 6]. Presumptively, hemodynamic variables improve faster in the presence of thrombolysis due to reduced plasma viscosity and improved microcirculatory reperfusion [7]. These effects substantially determine the degree of derangement of vital organ function and possibly counteract reperfusion disorders and postischemic-anoxic encephalopathy [8].

As the results of thrombolytic therapy during CPR of non-traumatic etiology are promising, we decided to investigate a subgroup of cardiac arrest patients with a known unfavorable outcome. This study was designed to evaluate the impact of thrombolytic therapy on return of spontaneous circulation (ROSC), duration of hospitalisation and outcome in patients with out-of-hospital resuscitation and asystole as the initial rhythm.

PATIENTS AND METHODS

STUDY BACKGROUND

The Emergency Medical Service (EMS) in Innsbruck, Austria, is an urban university-affiliated system, that serves a population of approximately 150 000 including semi-rural areas in the close vicinity. During the entire period of data collection, the EMS was two-tiered. In emergency cases the dispatcher immediately sent an ambulance with rescue personnel able to provide basic care including chest compression and bag ventilation with 100% oxygen. Simultaneously, he dispatched the Advanced Cardiac Life Support (ACLS) team, consisting of an emergency physician from the Department of Anaesthesia and Critical Care Medicine together with two emergency personnel trained in advanced emergency care. Evaluation of initial rhythm was performed by the emergency physician. All CPR patients underwent orotracheal intubation and mechanical ventilation. Peripheral intravenous access, preferably via the external jugular vein, was placed for drug administration.

STUDY DESIGN

A retrospective data analysis was conducted of 177 out-of-hospital cardiac arrests with asystole as the initial rhythm. Patients who underwent attempted resuscitation by the

Emergency Medical Service (EMS) in Innsbruck, Austria, between 1 January 1993 and 31 December 1998, were the subjects of this investigation. Patients who received recombinant tissue plasminogen activator (rt-PA) during CPR were compared to controls, who were closely matched in a 1:3 ratio according to arrival status (age, gender, witnessed arrest, bystander CPR). Computerized documentation of EMS data followed the Utstein style for uniform data reporting [9]. Operating sequence of resuscitation was according to the guidelines of the European Resuscitation Council [10]. Criteria for inclusion were: cardiac arrest of non-traumatic etiology in adult patients from 30 to 80 years of age with asystole as the initial finding on electrocardiogram. Patients with obvious non-cardiac disease such as trauma, drowning, suicide, drug overdose, intoxication, or known terminal illness were excluded. Data were collected from the ambulance case records, resuscitation charts, and hospital discharge letters. Information collected included patient demographic characteristics, intervals (time from call to ambulance arrival on scene, time from CPR onset to arrival in the Emergency Department) recorded in the pre-hospital setting, hospitalization, and the final outcome of patients who survived.

ADMINISTRATION OF RT-PA

Alteplase (Actilyse , Boehringer Ingelheim) was administered as 15-mg bolus over one minute followed by continuous infusion according to the Neuhaus schedule [11]. Following administration of rt-PA, resuscitation was continued until spontaneous circulation was achieved at least for another 20 to 30 minutes to allow proper thrombolytic activity. As the acceptance of thrombolytic therapy under out-of-hospital conditions varied among the emergency physicians, administration and onset of thrombolytic therapy depended on the emergency physician's clinical judgement and was not randomly assigned.

STATISTICAL ANALYSIS

Data analysis was performed by means of the test, and the T-test using SPSS v9.0 (SPSS Inc., Chicago, Illinois). Differences were regarded as statistically significant at $p < 0.05$. This study was approved by the institutional review committee. Procedures followed were in accordance with institutional guidelines.

RESULTS

A total of 177 OHCA patients with asystole as the initial rhythm presenting to the EMS were identified over a six-year period from January 1993 to December 1998. Thirty-four patients who received rt-PA during CPR were compared to 102 controls. There were no statistically significant differences for age or gender with regard to the outcome of resuscitation. Delay of ACLS was comparable in both groups. The EMS took an average of 6.6 +/- 3.1 minutes to arrive at the scene from the time of call. The average interval from onset of CPR until hospital admission was 61.6 +/- 15.3 minutes for patients in the study group and 45.7 +/- 15.8 minutes (P=0.698) for controls (Table 1).

Figure 1

Table 1: Arrival status, place of emergency and antithrombosis treatment for 34 patients in the treatment group and for 102 controls

Parameter	lysis (n=34)	control (n=102)	*P*
Arrival status			
Age, yrs (SD)	60.4 (11.8)	61.9 (12.4)	0.833
Male/female	29/5	86/16	0.891
Collapse witnessed (%)	17 (50)	32 (31)	0.329
Bystander CPR provided (%)	7 (21)	23 (23)	0.807
Call-response interval, min (SD)	6.1 (3.1)	6.7 (3.1)	0.656
CPR-admission interval, min (SD)	61.6 (15.3)	45.7 (15.8)	0.698
Place of emergency			
Private home (%)	18 (53)	68 (67)	0.151
Public (%)	6 (18)	17 (17)	0.895
Workplace (%)	3 (9)	3 (3)	0.148
Other (%)	7 (21)	14 (14)	0.338
Administration of antithrombotics			
Acetylsalicylic acid (%)	10 (29)	5 (5)	0.001
Heparin (%)	7 (21)	2 (2)	0.001

Male:female ratio was 5.5. Cardiac arrest was witnessed in 49 cases (34%), and bystander CPR was started in 30 cases (21%) out of all patients studied.

Of the 34 patients who received rt-PA treatment 23 regained sustained spontaneous circulation (68% vs. 33% in controls; p=0.001). Ten patients from the lysis group survived the first 24 hours (29% vs. 14% in controls; p=0.038), while only four survived more than ten days (12% vs. 5% in controls; p=0.163). Hospitalization lasted up to 29 days (2.4 +/- 4.7 days vs. 1.1 +/- 4.5 days in controls; p=0.071) (Table 2). Ultimately, three patients from the treatment group were discharged from hospital (9% vs. 3% in controls; p=0.570): two returned home and one was referred to another hospital. One patient from the control group was discharged home and two were admitted to rehabilitation units.

Figure 2

Table 2: Return of spontaneous circulation, 24-hour survival and outcome for 34 patients in the treatment group and for 102 controls

Parameter	lysis (n = 34)	control (n = 102)	*P*
Return of spontaneous circulation			
Spontaneous circulation restored (%)	23 (68)	34 (33)	0.001
Survival >24 hours (%)	10 (29)	14 (14)	0.038
Survival >10 days (%)	4 (12)	5 (5)	0.163
Survival to discharge	3 (9)	3 (3)	0.570
Bleeding complications on autopsy	(n = 15)	(n = 13)	
Intracerebral hemorrhage	0	1	
Subarachnoidal hemorrhage	1	0	
Ruptured aortic aneurysm	0	1	
Pericardiac tamponade	0	1	
Intramuscular bleeding	1	0	

In 28 of the 51 patients who died during hospitalization (55%) a detailed autopsy was performed. Autopsy reports available for 15 patients with rt-PA treatment revealed severe bleeding complications in two patients (13%). One patient suffered acute subarachnoidal hemorrhage and one patient developed profound intramuscular bleeding between the pectoral muscles on both sides of the chest. The control group included one patient with intracranial hemorrhage and one patient with ruptured aortic aneurysm and cardiac tamponade (Table 2).

DISCUSSION

The findings of this retrospective data analysis of a single-city six-year observational experience indicate that thrombolytic therapy may be beneficial in patients with OHCA and asystole. ROSC and 24-hour survival were more commonly observed under rt-PA treatment.

There are of course certain limitations on this study. The number of patients investigated is small despite a long observation period. This implies limited statistical power to validate the hypothesis that administration of thrombolytic agents can improve outcome, even under unfavorable circumstances. Treatment was not randomly assigned , but optional at the discretion of the treating emergency physician, which implies potential biases: outcome may be affected by factors related to the decision of administering thrombolytics. Although matched regarding age, gender and frequency of witnessed arrest and bystander CPR, selection bias cannot be completely ruled out. Quality of bystander CPR was not assessed although crucial for outcome, in particular when arrival of the advanced life-support team is delayed. Finally, we are aware that in a few cases enrolled in this study drug overdose or intoxication leading to cardiac arrest might have gone undiagnosed.

Conventional CPR procedures without the presence of protective factors e.g. hypothermia, are rarely effective in OHCA and asystole [1]. Although increased ROSC rate means that more people with spontaneous circulation are brought to the hospital, the outcome is still poor. As permanent brain damage following cardiac arrest and resuscitation is mostly determined by the duration of low perfusion and temperature, the first hours after OHCA and CPR are crucial in preventing reperfusion disorders and postischemic-anoxic encephalopathy [8]. Alternative methods such as hemodilution, hypertensive reperfusion, administration of antioxidants, emergency cardiopulmonary by-pass and mild postarrest hypothermia are further treatment options under discussion and ongoing investigation [12]. Peter Safar, the famous visionary of emergency medicine, even advocates suspended animation for prolonged preservation of viability to improve the prognosis of OHCA [8].

Major bleeding complications after CPR were reported to be as high as 5%-10% and to be slightly increased when thrombolytics were administered [13]. This corresponds with the findings of our study where two out of 15 deceased patients had developed major bleeding complications. This comparatively low rate of complications is particularly remarkable, as the overall number of anticipated CPR-associated fractures is anticipated to be high [14]. Despite the fact that one of the 34 patients in the treatment group experienced an acute subarachnoidal hemorrhage, thrombolytic treatment should not be withheld for OHCA patients [5]. Prehospital administration of alteplase is regarded to be safe and effective under CPR conditions [2,4].

Most studies of thrombolysis during CPR are of a retrospective nature.

In a randomized, double-blind, placebo-controlled study of tissue plasminogen activator in cardiac arrest, Abu-Laban et al. failed to find beneficial effects in 117 patients with pulseless electrical activity (PEA) [15]. The sole survivor of a 233-person cohort, however, had indeed received thrombolytic therapy. Survival among patients suffering from PEA is regarded to be very poor, especially among elderly unwitnessed cases and persons who did not receive bystander CPR [16]. In addition, thrombolytics were given late in the process of attempted resuscitation. Böttiger et al. in a prospective study of thrombolysis during CPR observed significantly improved ROSC and 24-hour survival in 40 patients who received rt-PA and heparin. Due to the low

number of patients there was no significant difference in hospital discharge [[2]].

A multicentred randomized prospective trial is planned by Böttiger et al. to investigate the impact of thrombolysis in cardiac arrest (TROICA). This will hopefully allow a more precise evaluation of whether increased frequency of ROSC is associated with improved survival state and better neurological outcome.

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