Outcome of out-of-hospital cardiac arrest after fibrinolysis with reteplase in comparison to the return of spontaneous circulation after cardiac arrest score in a geographic region without emergency coronary intervention

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Received February 11, 2016; Accepted December 1, 2016

DOI: 10.3892/etm.2017.4155

Abstract. Coronary occlusion and pulmonary embolism are responsible for the majority of cases of out-of-hospital cardiac arrest (OHCA). Despite previous favourable results of pre-hospital fibrinolysis in cases of OHCA, the benefit could not be confirmed in a large controlled study using the fibrinolytic tenecteplase. For reteplase (r-PA), there are hardly any data regarding pre-hospital fibrinolysis during ongoing resuscitation. The present study reported results using r-PA therapy in a German physician-supported Emergency Medical Services system. The data of OHCA patients who received pre-hospital fibrinolytic treatment with r-PA after an individual risk/benefit assessment were retrospectively analysed. To assess the effectiveness of this approach, the rate of patients with a return of spontaneous circulation (ROSC) was compared with the corresponding figure that was calculated with the help of the RACA (ROSC after cardiac arrest) score. The RACA algorithm predicts the probability of ROSC based on data from the German Resuscitation Registry. Further outcome data comprised hospital discharge rate and neurologic status at discharge. From 2001 to 2009, 43 patients (mean age, 58.5 years; 65.1% male; 58.1% ventricular fibrillation) received r-PA. Of these, 20 patients (46.5%) achieved ROSC, compared to a probability of 49.8% according to the RACA score (P=0.58). A total of 8 patients (18.6%) were discharged alive, including 5 (11.2%) with a good neurological outcome. For the analysed small patient collective, pre-hospital r-PA did not offer any benefits with regard to the ROSC rate. Further analyses of larger patient numbers on a nationwide registry basis are recommended.

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Key words: out-of-hospital cardiac arrest, cardiopulmonary resuscitation, reteplase, fibrinolysis, emergency medical services

Introduction

Although the prognosis of patients with out-of-hospital cardiac arrest (OHCA) has improved in certain parts of the world in recent years, 85-90% of patients still do not survive (1-4). Intravascular thrombi in coronary or pulmonary arteries are the most frequent cause of OHCA (5,6). In addition, massive activation of the coagulation system and disturbances of the microcirculation occur during circulatory arrest (7-9). For the majority of patients affected, fibrinolysis is therefore a pathophysiologically well-founded therapeutic option whose effectiveness has been shown in animal experiments (10,11). However, the positive results of several smaller prospective studies (12,13), case series studies (14,15) and one meta-analysis (16) on pre-hospital fibrinolysis in the case of OHCA could not be confirmed in a large randomised-controlled multicentre study (Thrombolysis in Cardiac Arrest, TROICA) where tenecteplase (TNK) was used (17). Possible reasons for this discrepancy between the TROICA and earlier studies include smaller effects of fibrinolysis if applied early during the course of resuscitation, differing proportions of patients with causal pulmonary embolism, lack of anti-coagulation and anti-aggregation co-medication and generally insufficient perfusion pressure during cardiopulmonary resuscitation (CPR) (17). Moreover, in the earlier studies, it appeared conceivable that patients with a more favourable prognosis were selected or that the statistical power was insufficient (18). Current CPR guidelines limit the indication for pre-hospital fibrinolysis

to patients with fulminant pulmonary embolism, whereas patients with other, potentially reversible causes of OHCA (e.g., coronary artery occlusion) should be considered for transport with ongoing CPR to a hospital that is suitable for causal therapy [mainly percutaneous coronary intervention (PCI)] (19). This strategy is supported by data from the German Resuscitation Registry, which indicate that in patients who were transported to a hospital offering PCI after the return of spontaneous circulation (ROSC), a significantly higher survival rate was observed than in patients treated in hospitals without PCI option (20). However, the question arises how transport with on-going CPR can be performed in practice in areas without a cardiology centre, which necessitates long transport times: Devices for automatic mechanical chest compression are not routinely used by Emergency Medical Services (EMS) systems, as outcome data after automatic mechanical chest compression, which often include the ongoing use of these devices during transport to the hospital, are not convincing (21).

It may therefore make sense to take a differentiated look at the value of pre-hospital fibrinolysis in the case of OHCA: If pre-hospital fibrinolysis leads to a higher probability of ROSC, this may enhance the number of cases in which patients in rural areas are subsequently transported to a cardiology centre.

As TNK, reteplase (r-PA) is a recombinant fibrinolytic, which is particularly attractive for pre-hospital application due to its bolus application (22). Regarding its usage in the case of on-going CPR, only single case reports have been available to date (23,24). The present study reported on the use of r-PA in patients with OHCA in the city of Kaiserslautern, Rhineland-Palatinate, Germany where emergency PCI was not regularly available at the time. For the evaluation of clinical effectiveness, the ROSC after cardiac arrest (RACA) score, which is an algorithm that allows for comparing the real ROSC rate with the expected probability of ROSC (25).

Materials and methods

EMS. The Kaiserslautern EMS System (Kaiserslautern, Germany) provides services to 161,249 residents of the city and the northern, eastern and southern part of the county of Kaiserslautern, in an area of 649.5 km^2. Among the inhabitants, 49.2% are male and 20.2% are older than 65 years (as of 31 December 2015). Since the implementation of an organized EMS system in the early 1970s until June 2007, ground-based, physician-staffed advanced life support (ALS) units provided single-tier support in the case of life-threatening emergencies. In July 2007, the system switched to a two-tiered approach with ambulances staffed by emergency medical technicians serving as the first tier in order to reduce response times. The emergency physicians deployed in the ALS units have a minimum of 30 months of experience in anaesthesiology, intensive care medicine and emergency medicine. They treat ~4,600 patients annually, including ~900 cases of acute coronary syndrome (ACS) and ~80 of OHCA, which corresponds to ~50 cases of OHCA per 100,000 residents per year. Automated mechanical chest compression systems were not used.

Fibrinolysis. Since emergency PCI was not routinely available in the region's hospitals, the emergency physicians were trained at pre-hospital fibrinolysis in 2001. As its application is simple (double bolus of 10 units given at 30-min intervals) and as this medication had already been introduced in the hospitals, r-PA (Rapilysin®; Hoffmann-La Roche, Grenzach-Wyhlen, Germany) was selected. The 3-h training of staff comprised the pharmacokinetics and -dynamics of r-PA as well as possible indications and contraindications, taking into account the aspect of 'off-label use' (Table I). In addition, CPR training was provided and repeated annually in accordance with the respective applicable guidelines of the European Resuscitation Council (26). Fibrinolysis was not administered as part of a clinical trial, but in everyday EMS work on the basis of an individual decision of the treating emergency physician in patients not responding to conventional treatment. All data were collected as part of the quality management process of the described EMS system. According to German law, no informed consent was therefore necessary.

Documentation. The following parameters were documented: Age, gender, medical history, performance of CPR by first responders, response time of EMS units, initial electrocardiogram rhythm, working diagnosis, duration of CPR, ROSC, time of application of lysis boli, co-medication, defibrillation, severe bleeding complications, in-hospital revascularising procedures, survival rate and neurological condition according to the Glasgow Pittsburgh Cerebral Performance Categories (27). Bleeding was classified as severe if representing a threat to the patient's life and/or requiring a blood transfusion or an endoscopic, interventional or operative procedure. The interval between the emergency call and the arrival of the EMS was determined on the basis of the electronic records of the dispatch centre; the time intervals after the arrival of the EMS were determined by reading the device-internal clocks of the defibrillator and an additional electronic stop watch. In-hospital progress as well as the times of release or death, were taken from patient files. The data were stored in a database in a pseudonymised manner. The evaluation was performed with the approval of the Ethics Commission of the State Chamber of Physicians (Mainz, Germany) Rhineland-Palatinate and the local study commission of the Westpfalz Hospital, Kaiserslautern, Germany (processing number 298E; decision dated 15th June 2015).

Statistical analysis. Descriptive statistical methods were used. For normally distributed data, mean values and standard deviations are represented; for non-normally distributed data, the median as well as the 25 and 75% percentiles, minimum and maximum are stated. The RACA score was calculated to determine the probability of ROSC. The multi-parametric algorithm underlying the RACA score was published in 2011 by Gräsner *et al* (25). The probability (p) of ROSC corresponds to the result of the formula $P=1/(1+e^{-X})$, where X is the sum of a constant and the following weighted single factors: Gender, age, cause of the arrest, observation of the arrest, site of the arrest (e.g., home, public location, physician's office, EMS vehicle), initial rhythm, presence

Table I. Guidelines for identifying and treating pre-hospital fibrinolysis in patients requiring resuscitation.

Criteria	Remarks
Principle	
Decisions always made on a case-by-case basis	Off-label use
Indications	
Circulatory arrest with the requirement of manual CPR and	In the case of PE, CPR for a minimum
Diagnosis of coronary occlusion or PE	of 60 min
Conditions under which fibrinolysis is likely to have lower chances of success	
Long interval without therapy	
Primary asystole	
Late start of lysis during the course of resuscitation	
Advanced chronic disease, e.g., pronounced dilated cardiomyopathy	
Contraindications	
Known bleeding disorder	Risk of bleeding not bearable or not
Known aortic aneurysm	predictable
Fresh severe trauma or surgery	
Clinically relevant bleeding as a consequence of resuscitation (e.g., from the bronchial system)	
Existing intracranial or intraspinal lesion (i.e., tumour, aneurysm, hemorrhage)	
Complete lack of information about medical history and current events	
Dosage	
Bolus 10 units	
If necessary: 2nd bolus after 30 min	
Co-medication	
Epinephrine and anti-arrhythmic agents according to current ERC guidelines	
In the case of ACS: 250 mg acetylsalicylic acid i.v.	Depending on individual bleeding risk
Heparin 60-70 IE/kg bw i.v.	Depending on individual bleeding risk

ACS, acute coronary syndrome; bw, body weight; i.v., intravenously; CPR, cardiopulmonary resuscitation; ERC, European Resuscitation Council; PE, pulmonary embolism.

or absence of first responder CPR and response time of EMS. For comparison of the predicted RACA score and the observed ROSC, the mean of RACA and the 95% confidence interval of the observed ROSC rate, and Fisher´s exact test (two-sided) were used. Data were processed using Microsoft Excel 2013 (Microsoft Corporation, Redmond, WA, USA), and PASW 18, 2009 (IBM SPSS, Armonk, NY, USA). $P<0.05$ was considered to indicate a statistically significant difference.

Results

Acute treatment of cardiac arrest. A total of 43 fibrinolyses were performed with on-going CPR. The mean patient age was 58.5±15.2 years and 28 of the patients (65.1%) were male. Coronary artery disease (CAD) was the most common pre-existing disease (Table II). 90.7% of the arrests had a cardiac cause. In 60.5% of the patients, a myocardial infarction could be observed. Only 32% of the arrests were observed. The EMS response time was 8 min on average. A total of 25 patients (58.1%) showed ventricular fibrillation and 23 (51.1%) were resuscitated by witnesses of the emergency (Table III). All patients were intubated; 38 (88.4%) received epinephrine

Table II. Baseline characteristics of the patients (n=43).

Characteristic	Value
Age (years)	
Mean ± standard deviation	58.5±15.2
Male gender	28 (65.1)
Medical history	16 (37.2)
Coronary artery disease	9 (20.9)
Previous transmural infarction	8 (18.6)
Cigarette smoking	9 (20.9)
Hypertension	6 (14.0)
Diabetes mellitus	7 (16.3)
Heart failure	
Unknown	17 (39.5)

Values are expressed as the mean ± standard deviation or the patient number with percentage in brackets as applicable.

Table III. Causes and circumstances of the cardiac arrest in the patient cohort (n=43).

Cause/circumstance	Value
Circumstance	
Witnessed collapse	14 (32.6)
Location of cardiac arrest	
At home	25 (58.1)
Public environment	13 (30.2)
Medical facility	2 (4.7)
Ambulance	4 (9.3)
Response time (min)	8.0±4.7
Causes	
Cardiac	39 (90.7)
Acute coronary syndrome	36 (83.7)
Confirmed myocardial infarction	26 (60.4)
Presumed myocardial infarction	10 (23.3)
Pulmonary embolism	3 (7.0)
Unknown	4 (9.3)
Initial rhythm	
VF	25 (58.1)
Asystole	16 (37.2)
PEA	0
Unknown	2 (4.7)
Initiation of CPR	
By bystander	22 (51.1)
By EMS	5 (11.6)

Values are expressed as the mean ± standard deviation or the patient number with percentage in brackets as applicable. CPR, cardiopulmonary resuscitation; E MS, emergency medical services; PEA, pulseless electric activity; VF, ventricular fibrillation.

Table IV. Management of cardiac arrest in the patient cohort (n=43).

Modality/treatment	Value
Intubation	43 (100)
Defibrillation	29 (67.4)
Number of defibrillation attempts	
Median (25-75% percentile)	6 (3-8)
Range	1-19
Epinephrine	38 (88.4)
Epinephrine dose (mg/min)	0.33±0.22
Amiodarone	20 (46.5)
Heparin	16 (37.2)
Acetylsalicylic acid	11 (25.6)
Acute treatment duration (min)	
CPR	46.0±18.4
CPR provided by ALS unit until first r-PA bolus	19.3±11.6
First r-PA bolus to second r-PA bolus	27.3±4.9
First r-PA bolus to ROSC	21.0±14.3

Values are expressed as the mean ± standard deviation or the patient number with percentage in brackets or the median, 25 and 75% percentile or minimum and maximum as applicable. ALS, advanced life support; CPR, cardiopulmonary resuscitation; ROSC, restoration of spontaneous circulation; r-PA, reteplase.

Table V. Clinical outcome in the patient cohort (n=43).

Parameter	n, (%)
Observed ROSC	20 (46.5), 95% CI: 31-62%
Probability of ROSC according to RACA algorithm	21.4 (49.8)[a]
ED admission	20 (46.5)
Hospital discharge	8 (18.6)
30-day survival	7 (16.3)
Neurologic status at discharge	
No or minor deficit (CPP 1/2)	5 (11.6)
Moderate deficit (CPC 3)	2 (4.7)
Coma (CPC 4)	0 (0)
Unknown	1 (2.3)

[a]Observed ROSC vs. RACA: Fisher's exact test: P=0.581. CI, confidence interval; CPC, cerebral performance category; RACA, ROSC in cardiac arrest; ROSC, restoration of spontaneous circulation; ED, emergency department.

and 29 (67.4%) were defibrillated. Only 16 patients (37.2%) were given heparin and 11 (25.6%) received heparin as well as acetylsalicylic acid. On average, r-PA was applied 19.3 min after the arrival of the emergency physician (Table IV).

Further course. 20 patients (46.5%) achieved ROSC, 8 (18.6%) survived until hospital discharge and 7 (16.3%) survived for 30 days. A total of 7 patients received PCI during the course of the treatment (Table V).

Bleeding complications. Two patients (4.6%) experienced severe bleeding: An initially asystolic 50-year-old patient with multiple cardiac risk factors without neurological deficits prior to the collapse was fibrinolysed as a myocardial infarction was suspected. However, an infarction could be excluded later on. With the patient in a persistent coma, a computed tomography (CT) scan was performed, revealing extensive subarachnoid hemorrhage (SAH), which was classified as the cause of the arrest. The patient succumbed to this cerebral event. In a 52-year-old woman, also with primary asystole, a pulmonary embolism was suspected. In her case, pre-hospital treatment additionally included administration of heparin. In the hospital she developed diffuse gastrointestinal bleeding. In addition, chest x-ray showed a haemothorax (probably as a consequence of CPR). She succumbed to kidney failure 3 days later.

Discussion

To the best of our knowledge, the present study presented the first analysis of fibrinolysis using r-PA with ongoing CPR in patients with OHCA. A total of 46.5 % of the patients achieved ROSC and 18.6% were discharged alive from the hospital. Although these figures are in accordance with ROSC rates in German registries ranging from 42.6-47.0%, and hospital discharge rates ranging from 9.8-10.4% in US registries to 13.8-16.6% in German registries (1-4), the comparison of the observed ROSC rate with the value expected on the basis of the RACA algorithm (49.8%) does not indicate a positive impact of r-PA on this important outcome parameter.

Therefore, although myocardial infarction was observed or suspected as the cause of the arrest in >80% of the patients, the results do not support the benefit of using fibrinolysis in achieving a higher ROSC rate in geographical regions with limited access to PCI and thus to increase the chances of subsequent interventional therapy in a cardiology centre. A comparable frequency of underlying myocardial infarctions has been reported by the TROICA study (17), where, as in the present study, fibrinolysed patients did not exhibit a higher ROSC rate than those who received standard treatment. Considering this high rate of thrombotic causes of OHCA as well as the fact that significant platelet activation is present during CPR (7), the question arises whether additional pre-hospital anti-coagulation and anti-aggregation therapy may be able to enhance the efficiency of fibrinolysis in cases of OHCA, without increasing the bleeding risk to an incalculable extent. In the present study, <40% of the patients received heparin as a pre-hospital treatment, and only ~25% had also received anti-aggregation treatment. In the TROICA study, using TNK as the fibrinolytic agent, heparin treatment and platelet inhibition had even been completely omitted in order to minimise the bleeding risk (17). In one study, significantly lower platelet aggregability was observed in the first h after administration of r-PA compared to alteplase (rt-PA), whereas after 24 h, the opposite effect occurred (28). In another study, adenosine diphosphate-induced platelet aggregation after administration of rt-PA in patients with stable CAD was lower than that observed with TNK or r-PA. However, fibrinogen concentration decrased after r-PA treatment, but not after TNK or rt-PA treatment (29). It therefore remains elusive to which extent a higher rate of anti-coagulation or anti-platelet co-therapy may contribute to a higher response rate to r-PA, or whether it may only increase the frequency of severe bleeding complications. The bleeding rate of 4.6% found in the present study corresponded exactly with the bleeding rate of 4.6% reported by a Swedish study on pre-hospital fibrinolysis by means of r-PA in patients with myocardial infarction not requiring CPR (30). In the Swedish study, 94.8% of the patients received heparin (initial bolus of 5,000 units, followed by continuous heparin infusion) and 79.2% received 300 mg oral aspirin. Compared to this, the rate of severe haemorrhage in patients who received fibrinolytic treatment for OHCA with rt-PA or TNK reported by previous studies ranges between 1.7 and 10% (16,17,31). Scenarios such as the case described above of the unexpected diagnosis of SAH are by no means rare and indicate the unresolved problem of excluding a primarily cerebral cause of OHCA in a pre-hospital setting (32).

Limitations. The present study comprised a relatively small number of patients with OHCA caused primarily by ACS, who were fibrinolysed by experienced emergency physicians following an individual risk/benefit assessment in the case of long-lasting CPR. This limits the transferability of the results with regard to EMS systems where the team has lower qualifications, where response times are shorter or longer, or for patients with other causes of cardiac arrest. Another potential limitation lies in the quality of CPR provided both by bystanders prior to the arrival of the EMS and by the EMS personnel. It is a fact that the emergency physicians in the present study received annual CPR training and had several years of clinical experience in advanced airway management. In addition, the frequency of defibrillation as well as the dosages of epinephrine and amiodarone administered show strong adherence to the CPR guidelines (26). However, no statement can be made regarding the actual quality of chest compressions, which is an essential criterion for the success of CPR (19,26). Finally, no autopsy was performed on the patients who did not achieve ROSC, and CT was not routinely performed on the patients admitted to the hospital, which may have decreased the diagnostic rate of CPR-associated injuries (33).

In conclusion, in the limited-size patient cohort examined in the present study, pre-hospital fibrinolysis with r-PA was not associated with a higher ROSC rate than that predicted by means of the RACA score. However, further studies using the RACA algorithm are recommended with larger patient numbers, i.e. from national CPR registry data, to check whether certain sub-categories of patients may potentially benefit from pre-hospital fibrinolysis with r-PA.

Acknowledgements

The authors express thanks to Ms. Astrid Niederle and Ms. Liubov Gorodilova of Fraunhofer IESE (Kaiserslautern, Germany) for their advice regarding statistical analysis.

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