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Clinical paper

Characteristics, diagnostic accuracy, and safety in patients receiving selective prehospital thrombolysis in out-of-hospital cardiac arrest: A retrospective cohort study

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Abstract

Objectives: Out-of-hospital cardiac arrest (OOHCA) carries a significant mortality implication despite optimal conventional therapies. To better understand the role of prehospital thrombolysis for OOHCA, we report the clinical outcomes, safety and enhanced care team diagnostic accuracy concerning selective thrombolysis by a physician-paramedic staffed air ambulance service.

Methods: A retrospective database review of electronic documentation was undertaken for all cases where thrombolysis was administered in OOHCA between January 2017 to April 2022 at Essex and Hertfordshire Air Ambulance Trust (EHAAT). Data collected included demographics, timings, pertinent clinical features, outcomes, and the treating team's suspected cause of arrest. For patients who died, cause of death was obtained from local coroners.

Results: 100 patients were identified and five survived to hospital discharge. The median (IQR) time from first cardiac arrest to thrombolysis was 58.5 min (44–75). The cause of death was available for 60 patients, among these 43% had suffered either a pulmonary embolus (PE) or myocardial infarction (MI). In patients who died of MI the critical care team correctly diagnosed this in 76.9% of cases, and of those who died of PE 92.3% were correctly diagnosed. However, the positive predictive value (PPV) of clinician diagnosis overall was only 36.7%.

Conclusion: Despite a high proportion of patients having a cause of OOHCA theoretically amenable to thrombolysis, survival to hospital discharge remains poor. Further work is required to better understand the future role and timing of prehospital thrombolysis in refractory OOHCA. Clinicians detected both MI and PE with high sensitivity but low PPV.

Keywords: Out-of-Hospital Cardiac arrest, Thrombolysis, Cardiac arrest, Clinicopathological correlation, Post mortem, Prehospital critical care

Introduction

Out-of-hospital-cardiac-arrest (OOHCA) is a frequent presentation encountered by emergency medical services (EMS) with approximately 34,407 OOHCA treated by EMS in England annually.[1] Thromboembolic events namely myocardial infarction (MI) or pulmonary embolus (PE), account for a significant proportion of OOHCA[2,3] and are widely regarded as 'reversible causes of cardiac arrest'.[4,5] Across Europe, survival rates for OOHCA remain below 10%[6] and therapeutic options for the management of thromboembolic disease during refractory OOHCA such as intra-arrest PPCI or ECMO are not yet widely available in the UK and were not available to this service during the data collection period.

Many enhanced prehospital care teams in the UK carry fibrinolytic agents in order to provide thrombolysis. However, with the establishment of primary percutaneous coronary intervention (PPCI) pathways, prehospital thrombolysis for MI is becoming less common[7]. Anecdotally, within the service in this study, the use of thrombolysis is now almost exclusively reserved for patients with

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suspected thromboembolic disease in cardiac arrest not responding to standard advanced life support (ALS). Less frequently it is considered in patients felt to be at risk of impending cardiac arrest or those who are unstable after return of spontaneous circulation (ROSC) in whom transport to PPCI, extracorporeal membrane oxygenation (ECMO) or thrombectomy services is not felt to be achievable.

There is scant evidence or expert consensus to support the use of thrombolytic agents in this context, especially when the suspected cause of arrest is cardiac or undifferentiated. Indeed, current International Liaison Committee on Resuscitation (ILCOR) and resuscitation council UK guidelines only support the use of thrombolysis in suspected or confirmed PE, not in suspected MI or undifferentiated patients.[4,5]

There is currently little in the literature about the accuracy of clinician diagnoses in the prehospital setting where access to diagnostic tools is limited. In this setting accurate diagnosis determines management plans and patient destination. In addition there are few studies reporting the cause of death in patients with refractory out of hospital cardiac arrest.

The objective of this retrospective observational study was to ascertain the characteristics of patients administered thrombolysis at EHAAT, evaluate outcomes and delineate causes of death in those that did not survive. Accuracy of clinician diagnosis was also assessed.

Methods

Study design

This was a retrospective observational cohort study. A retrospective database review of prospectively completed electronic documentation on HEMSbase™ (Medic One Systems, Tadworth, UK) was carried out.

Setting

EHAAT is paramedic-physician helicopter emergency medicine service (HEMS) based in the East of England, a mixed urban and rural area of the UK. It responds by air or rapid response vehicle to critically ill and injured patients of all ages. The service has operated a 24 hour service since 7th October 2019. Medical emergencies account for around 39% of the caseload and approximately 43% of these are activations to an OOHCA. Dispatch to adult cardiac arrests is at the discretion of a HEMS paramedic (or clinical dispatcher if no HEMS paramedic is available), based in the ambulance Emergency Operations Centre, if they feel critical care input may be of benefit. This may be from brief interrogation of the 999 call or after discussion with an ambulance crew on scene.

During the study period the service carried Tenecteplase 10,000 iu as a fibrinolytic agent, this has historically been a preferred prehospital agent due to the practicalities of bolus dosing in acute MI.[8] Of note however, alteplase is the recommended agent in current national PE guidelines and is also given as a bolus dose in PE resulting in cardiac arrest or shock.[9] All patients to whom Tenecteplase was administered during the study period were administered it having suffered OOHCA.

There is a Standard Operating Procedure (SOP) within the service for OOHCA which describes the use of thrombolysis as first line treatment in PE with shock. It also states that thrombolysis has limited evidence base in cardiac arrests related to acute coronary syndrome (ACS) either intra-arrest or post ROSC, and if considered a consultant phone call is essential. The diagnosis of PE or ACS is made by the clinicians on scene based on history, examination, analysis of the ECG (pre arrest or in ROSC) and echo findings. From September 2018 all cases were discussed with a prehospital care consultant doctor prior to administration of Tenecteplase. Those patients in this series thrombolysed in ROSC had had recurrent arrests or were extremely unstable post ROSC. UK resuscitation guidelines suggest considering CPR for 60–90 min post administration of thrombolytic drugs for PE.[4] Where resuscitation was stopped prehospitally the decision around duration of CPR post thrombolysis was made by the attending clinicians based on history and clinical course, with telephone support from a Prehospital Care Consultant available.

Participants

All cases where Tenecteplase had been given in the setting of OOHCA between January 2017 to April 2022 were identified and data was anonymised and extracted for analysis. Data including demographics, timings, pertinent clinical features and prehospital outcome, as well as the treating team's suspected cause of arrest (MI or PE) were recorded. Where any of this information was not captured by dropdown sections of the record, the free-text notes were reviewed to maximise data capture.

Outcome data beyond the prehospital phase was obtained from HEMSbase™ notes, East of England Ambulance Service Trust (EEAST) cardiac arrest data and follow up obtained by the EHAAT patient and family liaison team.

The aims of this study were to describe clinical outcomes, safety and enhanced care team diagnostic accuracy in the prehospital setting for patients administered prehospital thrombolysis as well as to better understand the disease profile of this refractory cardiac arrest population. Therefore more detailed in-hospital follow up of survivors and causes of death for non-survivors were collected where available. For the patients who died within Essex and Hertfordshire coronial districts, cause of death was ascertained from local coroners.

This project was carried out as a retrospective service evaluation and was deemed by local research protocols not to require ethical approval. A STROBE checklist was followed for this project.

Statistical methods

Data was analysed using SPSS statistics (version 30). A Shapiro–Wilk test was performed to assess distribution of data. All parameters were not normally distributed.

Data are presented as counts with percentages or median with inter-quartile range. Sensitivity and Positive Predictive Value (PPV) were used to assess diagnostic accuracy.

Results

Participants

Out of 2043 medical arrests attended by EHAAT during the study period, 100 patients received thrombolysis (4.89% of attended arrests).

Patient and arrest characteristics can be seen in Table 1. All patients given thrombolysis during the study period were given it in the context of out of hospital cardiac arrest.

Prehospital data were available for all patients but 3 patients were lost to follow up after hospital admission.

Table 1 – Patient and arrest characteristics.

Variable	Results (n (%) or median (IQR))
Age (years)	59.1 (48–68.75)
Sex	Male: 78 (78%)
Initial rhythm	Shockable: 53 (53%)
	VF: 46 (46%)
	VT: 2 (2%)
	AED shockable: 5 (5%)
	Non-shockable: 47 (47%)
	PEA: 32 (32%)
	Asystole: 13 (13%)
	AED non-shockable: 2 (2%)
Location of arrest	Private residence: 62 (62%)
	Public place: 29 (29%)
	Industrial/workplace: 6 (6%)
	Sport/recreation/other: 3 (3%)
Witnessed arrest	Yes: 95 (95%)
Immediate CPR	Yes: 88 (88%)
Total shocks (for those in a shockable rhythm)	6 (3–10)
Arrest rhythm at time of thrombolysis	PEA: 51 (51%)
	VF: 19 (19%)
	Asystole: 7 (7%)
	Not recorded: 14 (14%)
Thrombolysed in ROSC	9 (9%)
Signs of life at time of thrombolysis	No: 74 (74%)
	Yes: 18 (18%)
	Not recorded: 8 (8%)

VF: Ventricular fibrillation. pVT: pulseless ventricular tachycardia. AED: Automated external defibrillator. PEA: Pulseless electrical activity. ROSC: Return of spontaneous circulation.

Timeline to thrombolysis

Information regarding HEMS dispatch and treatment times in relation to the time of arrest can be seen in Table 2. Two patients who arrested with HEMS already in attendance received thrombolysis in 11 and 32 min. The timelines for the five survivors are reported separately in Table 3.

Clinical outcomes

29 patients were pronounced life extinct in the prehospital phase; 53 were transported in arrest/intermittent arrest (two survived to discharge, 49 died in hospital and two had no in-hospital follow up available) and 18 were transferred in ROSC (three survived to discharge, 14 died in hospital and one had no in-hospital follow up available). Of the patients who were lost to follow up after hospital admission one was transported in sustained ROSC, one with intermittent arrests and one in arrest throughout.

Seventy-one patients (71%) were transported to hospital with 18 patients (25.4%) in a sustained ROSC. Following exclusion of three patients for whom there was no follow up after hospital admission, five patients (5.2%) survived to hospital discharge.

Of the five survivors, three were discharged neurologically intact and two survived to discharge with unclear neurological outcome. Four survivors had a presenting rhythm of VF and one was in PEA. MI was the suspected cause of their arrest in four, and one had no indication documented. Four were thrombolysed in arrest and one post ROSC. More detailed in-hospital diagnostic information was available for two of the patients. One patient with suspected MI had normal coronary arteries on formal angiography and was thought to have a primary cardiomyopathy driven arrhythmia. The second patient had a gated computed tomography scan which did not show any coronary artery atheroma or PE but no further follow up was available.

Cause of death

Cause of death was obtained from coroners' records for 60 of the 85 patients who died in Essex and Hertfordshire coronial districts, where available these were from post mortem findings. If no post mortem

Table 2 – Timeline information.

Time interval	Time in minutes Median (IQR)
999 to HEMS dispatch	16.5 (7–32)
HEMS dispatch to patient side	21 (17–25)
Arrest to HEMS arrival*	32 (24–46)
With patient to thrombolysis	24 (16–32)
Time of arrest to thrombolysis	58 (44–75)

* excluding two patients where patient arrested in the presence of HEMS.

Table 3 – Timeline details for the patients who survived to hospital discharge.

Survivor	999 – HEMS dispatch (mins)	HEMS dispatch to patient side (mins)	Arrest to HEMS arrival (mins)	With patient to thrombolysis (mins)	Time of arrest to thrombolysis (mins)
1	16	27	27	13	40
2	10	11	15	45	60
3	7	21	32	25	57
4	7	18	25	9	34
5	6	19	27	4	31

had taken place the cause of death on the Medical Certificate of Cause of Death was used.

13 died due to PE and 13 due to MI. 30 had a cause of death of other non-occlusive cardiac causes, most commonly: Acute cardiac failure, coronary artery disease or ischaemic heart disease. Cardiomyopathy, myocardial rupture, mitral valve prolapse and primary arrhythmia were other cardiac causes of death identified.

Four patients had a terminal aortic emergency (Aortic dissection or aneurysm) identified at post mortem. These patients were all in a non-shockable rhythm at the time of their arrest (three were in PEA and one in asystole).

There were no reports of catastrophic bleeding in any of these patients and in particular there were no reported cases of intracranial haemorrhage.

Clinician diagnostic accuracy

The suspected cause of arrest documented by the prehospital team was MI in 62 and PE in 33. Five patients did not have a suspected cause of arrest documented.

Overall, twenty-two of the provisional diagnoses made prehospital by the enhanced care team matched the cause of death recorded by the coroner with an overall PPV of 36.7%. Thirteen patients had a confirmed MI, 10 of these were correctly diagnosed by the enhanced team with a sensitivity of 76.9% and a PPV of 31%. Thirteen had a confirmed PE and 12 of these were correctly diagnosed by the enhanced care team with a sensitivity of 92.3% and PPV of 48% demonstrating high sensitivity but low PPV of clinicial diagnosis in this selected group of patients with OOHCA.

Discussion

In this retrospective cohort study, there was a poor rate of survival to hospital discharge in patients who had received thrombolysis. These outcomes occurred despite a high preponderance of aetiologies found at post mortem that would likely be amenable to fibrinolytic therapy. For the remaining patients without an acute thromboembolic aetiology, thrombolysis likely had negligible impact on outcomes. Interestingly four patients (6.7%) had acute aortic emergencies found post mortem; whilst this high incidence in refractory OOHCA is an important consideration for enhanced care teams, thrombolysis is unlikely to have had an additional mortality implication given their extremely poor prognosis. Reassuringly, catastrophic bleeding caused by thrombolysis was not identified in any patients with coronial follow up.

In 2022 *Alshaya et al.* published a systematic review and meta-analysis of evidence pertaining to the administration of fibrinolytic agents to patients in cardiac arrest due to confirmed/presumed cardiac aetiology or PE.[10] A trend towards increased rates of ROSC, survival at 24 h, 30 days and to discharge was reported, although none of these benefits were statistically significant. There was also an increased rate of bleeding in patients who received thrombolysis which was statistically significant and is of concern. This is especially true in the undifferentiated prehospital patient (who may be in cardiac arrest due to a haemorrhagic cause, for example subarachnoid haemorrhage, aortic or traumatic pathologies) and also in those receiving prolonged mechanical chest compressions, known complications of which include injury to the thoracic and abdominal organs.[11] Despite the lack of high certainty evidence and concerns regarding bleeding complications there are numerous case reports of patients receiving thrombolysis intra-arrest for both proven or presumed PE or MI resulting not only in ROSC but also good neurological outcomes, even in the context of prolonged low flow times.[11–16]

The sustained ROSC and survival rates described in this study, compare unfavourably to those reported elsewhere in the literature. A study from France investigating effects of thrombolysis in OOHCA reported a significantly higher survival to hospital admission rate in those receiving thrombolysis of 47.7%, compared to 23.6% in those who did not receive it. However, survival past hospital admission was not studied.[17] Another study which looked retrospectively at outcomes of patients with PE found 30-day survival post thrombolysis was 16% in those who suffered OOHCA as a result of their PE compared to 6% in those who were not thrombolysed.[18] The large urban–rural geographical footprint of EHAAT operations resulted in prolonged low flow times at the point of thrombolysis administration, and may partially explain these results. The correlation between increased duration of CPR and increased mortality has been previously reported.[19] Further work is needed to study the impact of this intervention if delivered earlier in the chain of survival.

The literature is however mixed with other RCTs and meta-analyses showing no statistically significant increase in survival when comparing placebo with prehospital thrombolysis for the treatment of OOHCA. With regard to bleeding complications these studies also reported an increase in bleeding events in those thrombolysed.[8,20,21] Bottinger et al reported increased intracranial haemorrhage events in survivors post thrombolysis but did not have cause of death or post mortem data for those who died.[21] The absence of reported bleeding complications or intracranial haemorrhage in the studied cohort is interesting. A lack of bleeding complications has also been reported in a recent registry study of patients receiving prehospital thrombolysis for OOHCA.[18]

This study utilised retrospective data, however, all data was recorded at the time of the event. All patients were treated by a single service with specific SOPs which may limit how applicable the findings are to other Prehospital care providers. In addition to the three patients where outcome could not be established, it was only possible to obtain detailed discharge summaries for one of the five patients who survived which limits our ability to understand any incremental benefit of thrombolysis in this group. The cause of death data was compiled of a mixture of hospital death certificates and post mortem outcomes. Therefore, there is potential that other medical causes of death would not have been identified and therefore recorded in this study.

Conclusion

This study describes clinical outcomes, safety and enhanced care team diagnostic accuracy in the prehospital setting for patients administered prehospital thrombolysis. 5% of patients administered thrombolysis survived to hospital discharge. No patients who underwent post mortem were found to have intracranial or intraabdominal/thoracic haemorrhage secondary to thrombolysis. Clinicians diagnosed both PE and MI with high sensitivity but low PPV.

CRediT authorship contribution statement

Anna Forbes: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Adam Pitcairn:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Rachael Harding:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Sarah McLachlan:** Writing – review & editing, Supervision, Investigation, Formal analysis, Data curation. **Gareth Grier:** Writing – review & editing, Writing – original draft, Supervision, Resources. **Peter Sherren:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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