Adrenaline to improve survival in out-of-hospital cardiac arrest: the PARAMEDIC2 RCT

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Scientific summary

The PARAMEDIC2 RCT

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Scientific summary

Background

Each year, the NHS treats ≈ 30,000 people who are experiencing out-of-hospital cardiac arrest. Overall survival rates are low (< 10%), falling further (to ≈ 3%) among patients who are unresponsive to initial treatments; such patients require treatment escalation to the use of drugs. Adrenaline has been used as a treatment for cardiac arrest for decades. The International Liaison Committee on Resuscitation examined the evidence for the use of adrenaline in cardiac arrest and identified uncertainty about the effects on long-term outcomes. Some recent, large, observational studies showed a pattern of worse neurological outcomes in patients who received adrenaline. These findings prompted an international call for a trial to examine the clinical effectiveness and safety of adrenaline as a treatment for out-of-hospital cardiac arrest.

Objectives

The primary objective of this trial was to determine the clinical effectiveness of adrenaline in the treatment of out-of-hospital cardiac arrest, measured as 30-day survival (i.e. the primary outcome). The secondary objectives of the trial were to evaluate the effects of adrenaline on survival, neurological outcomes and health-related quality of life among survivors, and to estimate the cost-effectiveness of adrenaline use.

Methods

Ethics and regulatory approvals

The trial was approved by the South Central Oxford C Research Ethics Committee (reference number 14/SC/0157) and the Medicines and Healthcare Products Regulatory Agency (EudraCT number 2014-000792-11). The trial was sponsored by the University of Warwick and was conducted in accordance with the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 [European Commission. *Clinical Trials – Directive 2001/20/EC*. URL: https://ec.europa.eu/health/human-use/clinical-trials/directive_en (accessed 23 September 2020)], The Medicines for Human Use Act (Clinical Trial) Regulations, Statutory Instrument 2004 No. 1031 and Amendment (No.2) Statutory Instrument 2006 No. 2984 [Great Britain. *The Medicines for Human Use (Clinical Trials) Regulations 2004*. London: The Stationery Office; 2004 (and amendment in 2006)].

The Confidentiality Advisory Group provided approval under regulation 5 of the Health Service (Control of Patient Information) Regulations 2002 [Great Britain. *The Health Service (Control of Patient Information) Regulations 2002*. London: The Stationery Office; 2002] to process patient-identifiable information without consent (reference number 14/CAG/1009).

Design

This was a pragmatic, randomised, allocation-concealed, placebo-controlled, parallel-group superiority trial and economic evaluation.

Inclusion and exclusion criteria

Patients were eligible if both of the following criteria were met:

1. cardiac arrest in out-of-hospital environment
2. advanced life support initiated and/or continued by ambulance service clinician.

Exclusion criteria at the time of arrest were as follows:

- known or apparent pregnancy
- known to be or apparently aged < 16 years
- cardiac arrest caused by anaphylaxis or life-threatening asthma
- adrenaline given prior to arrival of ambulance service clinician.

In London Ambulance Service, traumatic cardiac arrests were also excluded, in accordance with local protocols.

Setting

Recruitment was undertaken in five NHS ambulance services in the UK (London Ambulance Service NHS Trust, North East Ambulance Service NHS Foundation Trust, South Central Ambulance Service NHS Foundation Trust, West Midlands Ambulance Service University NHS Foundation Trust and Welsh Ambulance Service NHS Trust). These ambulance services serve a mix of urban and rural locations in England and Wales, covering a population of 24 million people.

Consent

Cardiac arrest leads to an immediate loss of mental capacity, so it was not possible to obtain informed consent from patients prior to enrolment. The time-critical nature of administering treatments for cardiac arrest meant that it was not practical to obtain informed consent from a personal or professional legal representative without the potential for causing harm through delaying patient treatment. In accordance with the European Union Clinical Trials Directive and the Statutory Instrument 2004/1031, we sought and obtained permission from a Research Ethics Committee to enrol patients prior to obtaining informed consent. Research staff sought written, informed consent from the patient or a legal representative for them to continue in the trial after the initial emergency had passed.

Resuscitation protocols and randomisation process

The NHS ambulance services followed the Joint Royal Colleges Ambulance Liaison Committee guidelines, which are based on the Resuscitation Council (UK) National Institute for Health and Care Excellence-accredited guidelines. The guidelines recommend that initial attempts at resuscitation should comprise initiation of cardiopulmonary resuscitation (chest compressions and ventilations) and defibrillation when indicated. For patients with non-shockable initial rhythms, adrenaline is recommended as soon as vascular access is obtained. For those with shockable initial rhythms, adrenaline is delayed until after the third shock is administered, if the patient remains in cardiac arrest.

The Pre-hospital Assessment of the Role of Adrenaline Measuring the Effectiveness of Drug administration In Cardiac arrest 2 (PARAMEDIC2) trial followed these guidelines. If a patient reached the point in the resuscitation protocol whereby adrenaline was indicated, they were randomly assigned to receive either parenteral adrenaline or saline placebo by the opening of a trial drug pack. Randomisation took place when a trial-trained paramedic opened an Investigational Medicinal Product pack that contained either 10 syringes of adrenaline (1 mg each) or matching placebo (0.9% saline). Patients were randomised to either adrenaline (intervention) or placebo (control) in a 1 : 1 allocation ratio. The adrenaline and placebo packs and syringes were identical in appearance; hence, clinicians, patients and trial personnel did not know whether any specific pack contained adrenaline or placebo.

Single doses of adrenaline or saline were administered every 3–5 minutes by an intravenous or intraosseous route. Clinicians were instructed to use only one treatment pack per patient (10 × 3-ml syringes). Treatments were continued until a sustained pulse was achieved, resuscitation was discontinued or care was handed over to a clinician at the receiving hospital.

Outcomes

The primary outcome was survival to 30 days.

The secondary outcomes were as follows:

- survived event (sustained return of spontaneous circulation, with spontaneous circulation until admission and transfer of care to medical staff at the receiving hospital)
- survival to hospital discharge (the point at which the patient is discharged from the hospital acute care unit, regardless of neurological status, outcome or destination) and to 3, 6 and 12 months
- neurological outcome (measured using the modified Rankin Scale) at hospital discharge and at 3 and 6 months (assessed at discharge using the Rankin Focused Assessment), and completed at 3 and 6 months via the simplified modified Rankin Scale questionnaire
- neurological outcomes (measured using the Informant Questionnaire on Cognitive Decline in the Elderly and 'Two Simple Questions') at 3 and 6 months
- health-related quality of life at 3 and 6 months (measured using the Short Form questionnaire-12 items and the EuroQol-5 Dimensions, five-level version)
- cognitive outcome at 3 months (measured using the Mini Mental State Examination)
- anxiety and depression at 3 months (measured using the Hospital Anxiety and Depression Scale)
- post-traumatic stress at 3 months (measured using the Post-traumatic stress disorder Checklist-Civilian version)
- hospital length of stay
- intensive care unit length of stay.

Economic evaluation

The primary economic evaluation was the incremental cost per quality-adjusted life-year gained from the perspective of the NHS and Personal Social Services.

The secondary economic evaluation considered the cost of critical care stay (level 2/3 days), the cost of hospital stay, utilisation of NHS and Personal Social Services resources after discharge and broader resource utilisation after discharge.

Data were collected on the health and social service resources used in the treatment of each trial participant during the period between randomisation and 6 months post randomisation.

An incremental cost-effectiveness analysis was performed, and results were presented using incremental cost-effectiveness ratios and cost-effectiveness acceptability curves, generated via seemingly unrelated linear regressions and non-parametric bootstrapping. A decision-analytic model was used to extrapolate economic outcomes beyond the trial-follow-up and to assess the cost-effectiveness of adrenaline over the lifetimes of cardiac arrest survivors. Long-term costs and health consequences were reduced to present values using discount rates recommended for health technology appraisal in the UK. A series of probabilistic sensitivity analyses were undertaken to explore the implications of parameter uncertainty on the incremental cost-effectiveness ratios.

Sample size and statistical analysis

The target sample size was 8000 participants, which was expected to give a width of the 95% confidence interval for the risk ratio of approximately 0.4 or slightly less; for a risk ratio of 1.25, the 95% confidence interval was 1.07 to 1.46, and for a risk ratio of 1.0, it was 0.84 to 1.19. During the conduct of the trial, the event rate for the primary outcomes was observed to be lower than that

originally expected. Modelling various scenarios, and noting that an absolute risk reduction of 1% had been used widely in resuscitation trials to define the minimal clinically important difference, it was concluded that the trial would still yield valuable information about the safety and clinical effectiveness of adrenaline if the observed survival rates continued to the end of the trial.

The primary analysis was performed with and without adjustment in the modified intention-to-treat population, which included all the patients who had undergone randomisation and were confirmed to have received the assigned intervention. Fixed-effect regression models were used to examine survival outcomes with and without adjustment. Variables included in adjusted analyses were age, sex, the time between the 999 call and the ambulance arriving at the scene, the time between the ambulance arriving and trial drug administration, the suspected aetiology of the cardiac arrest, the initial heart rhythm, whether or not the event was witnessed, and whether or not a bystander undertook cardiopulmonary resuscitation.

The Hodges–Lehmann method was used to estimate median differences with 95% confidence intervals for length-of-stay outcomes. In cases in which the proportional odds assumption was violated in modelling of the score on the modified Rankin Scale, partial proportional odds models were used. Scores on the modified Rankin Scale were also analysed as a binary outcome (with scores of 0–3 classified as 'good' and scores of 4–6 classified as 'poor'). Other secondary outcomes (including quality of life and neurological and cognitive functions) were summarised by treatment arm. To aid in interpretation, we included a Bayesian analysis for the primary outcome and for survival with a favourable neurological outcome.

Patient and public involvement

A community engagement event was held prior to the start of the trial to assess the need and acceptability of the trial and to explore which outcomes were most important to patients. Information about the trial was disseminated through both health-care and non-health-care settings. Throughout the trial, we met regularly with patient and public groups, including a patient and public advisory group. A lay member of the trial team and two independent patient and public representatives served on the Trial Management Committee and Trial Steering Committee, respectively.

Results

From December 2014 to October 2017, 8014 patients were assigned either to the adrenaline arm ($n = 4015$) or to the placebo arm ($n = 3999$). At 30 days, 130 out of 4012 patients (3.2%) in the adrenaline arm and 94 out of 3995 patients (2.4%) in the placebo group were arm (adjusted odds ratio for survival 1.47, 95% confidence interval 1.09 to 1.97). For secondary outcomes, a larger proportion of participants in the adrenaline arm than in the placebo arm survived to hospital admission (23.6% vs. 8.0%; adjusted odds ratio 3.83, 95% confidence interval 3.30 to 4.43). The rate of favourable neurological outcome at hospital discharge was not significantly different between the arms (2.2% in the adrenaline arm vs. 1.9% in the placebo arm; adjusted odds ratio 1.19, 95% confidence interval 0.85 to 1.68). The pattern of improved survival, but no significant improvement in neurological outcomes, continued to 6 months. By 12 months, survival in the adrenaline arm was 2.7%, compared with 2.0% in the placebo arm (adjusted odds ratio 1.38, 95% confidence interval 1.00 to 1.92). A Bayesian analysis found a 37% probability that the absolute rate of survival was > 1% in the adrenaline arm and a 1.9% probability for a > 1% improvement in favourable neurological outcome. An adjusted subgroup analysis did not identify any significant interactions.

Severe neurological impairment (a score of 4 or 5 on the modified Rankin Scale) at discharge was more common among survivors in the adrenaline arm than among those in the placebo arm [39/126 (31.0%) vs. 16/90 (17.8%) patients, respectively]. The number of patients with severe neurological impairment decreased through to 6 months, although evaluation was limited by greater loss to follow-up.

Examining health-related quality of life up to 6 months after randomisation and examining cognitive function, anxiety/depression or post-traumatic stress to 3 months showed that there was significant functional impairment in cardiac arrest survivors, compared with the normal population. One-third to half of patients reported that they needed help from someone with everyday activities. For most, this was a new situation after their cardiac arrest. Fewer than half reported having made a full mental recovery after their cardiac arrest. Although underpowered, the pattern of impairment suggested greater disability in the adrenaline group.

The incremental cost-effectiveness ratio for adrenaline was estimated at £1,693,003 per quality-adjusted life-year gained over the first 6 months after the cardiac arrest event, and £81,070 per quality-adjusted life-year gained over the lifetime of survivors. The associated adjusted mean incremental net monetary benefit of adrenaline at cost-effectiveness thresholds of £30,000 per quality-adjusted life-year was −£1282 (95% confidence interval −£1733 to −£831) at 6 months and −£1118 (95% confidence interval −£2776 to £487) over the lifetime of survivors.

Conclusions

Findings from this research indicate that adrenaline was effective at restarting the heart and sustaining circulation to hospital admission following out-of-hospital cardiac arrest. Adrenaline also improved long-term survival, but did not improve survival with favourable neurological outcome. The incremental cost-effectiveness ratio per quality-adjusted life-year exceeds the level usually supported by the NHS.

Further research is required to better understand patients' preferences in relation to survival and neurological outcome after out-of-hospital cardiac arrest and to aid interpretation of the trial findings from a patient and public perspective. Further research examining the time to adrenaline administration and the route of administration (intravenous or intraosseous) may provide additional insights to the trial's findings.

Trial registration

This trial is registered as ISRCTN73485024 and EudraCT 2014-000792-11.

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This report

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