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ORIGINAL

The influence of time to adrenaline administration in the Paramedic 2 randomised controlled trial

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Abstract

Purpose: To examine the time to drug administration in patients with a witnessed cardiac arrest enrolled in the Pre-Hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest (PARAMEDIC2) randomised controlled trial.

Methods: The PARAMEDIC2 trial was undertaken across 5 NHS ambulance services in England and Wales with randomisation between December 2014 and October 2017. Patients with an out-of-hospital cardiac arrest who were unresponsive to initial resuscitation attempts were randomly assigned to 1 mg intravenous adrenaline or matching placebo according to treatment packs that were identical apart from treatment number. Participants and study staff were masked to treatment allocation.

Results: 8016 patients were enrolled, 4902 sustained a witnessed cardiac arrest of whom 2437 received placebo and 2465 received adrenaline. The odds of return of spontaneous circulation decreased in both groups over time but at a greater rate in the placebo arm odds ratio (OR) 0.93 (95% CI 0.92–0.95) compared with the adrenaline arm OR 0.96 (95% CI 0.95–0.97); interaction OR: 1.03, 95% CI 1.01–1.05, $p = 0.005$. By contrast, although the rate of survival and favourable neurological outcome decreased as time to treatment increased, the rates did not differ between the adrenaline and placebo groups.

Conclusion: The rate of return of spontaneous circulation, survival and favourable neurological outcomes decrease over time. As time to drug treatment increases, adrenaline increases the chances of return of spontaneous circulation. Longer term outcomes were not affected by the time to adrenaline administration. (ISRCTN73485024).

Keywords: Adrenaline, Advanced life support, Cardiac arrest, Drugs, Timing

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Introduction

Adrenaline (epinephrine) has been used as a treatment for cardiac arrest for over 50 years [1]. Observational studies found that adrenaline was effective at achieving a return of spontaneous circulation (ROSC) and short term survival, but there was uncertainty about its effects on long-term survival and survival with a favourable neurological outcome [2]. The PARAMEDIC2 study was a large randomised, double blind, placebo controlled trial which evaluated the effect of standard dose adrenaline (1 mg every 3–5 min) in adults with out of hospital cardiac arrest (OHCA) [3]. The trial found that adrenaline increased ROSC and survival to 30 days/hospital discharge but did not find evidence of improved survival with a favourable neurological outcome at hospital discharge.

Early descriptions of the use of adrenaline as an adjunct to assist with resuscitation from cardiopulmonary arrest emphasised the importance of early administration [4, 5]. One possible explanation for the failure of adrenaline to improve neurological outcomes may be if treatment is administered too late after the onset of cardiac arrest. This hypothesis is supported by animal studies [6–8] and observational studies of cardiac arrest both in- and out-of-hospital [9, 10], which suggest better outcomes the earlier that adrenaline is administered. However, the findings of observational studies need to be interpreted with caution because of likely confounding. Resuscitation time bias occurs when interventions are given during the treatment of cardiac arrest (e.g. tracheal intubation, drug administration) [11]. As outcomes are worse the longer the duration of a cardiac arrest, late administration of the intervention is biased by the fact that the duration of cardiac arrest has been longer.

The influence of resuscitation time bias may be reduced by the analysis of time to intervention from double blind, randomised controlled trials, where we would expect no difference in the timing of drug administration between adrenaline and placebo groups. The aim of this paper is to examine the effect of time to drug administration in the PARAMEDIC2 study on ROSC, survival to discharge and neurological outcome [3].

Take-home message

Rates of survival and favourable neurological outcome decrease the longer a patient is in cardiac arrest. Thus, the duration of cardiac arrest, rather than time to drug administration, is the key determinant of outcome.

Methods

Study design

The background to the trial, methods and baseline characteristics of the randomised patients have been previously reported [3, 12].

The protocol was approved South Central–Oxford C Research Ethics Committee and the Medicines and Healthcare Products Regulatory Authority. Trial oversight was provided by independent trial steering and data monitoring committees. The trial was designed and conducted in accordance with the principles of Good Clinical Practice, the Directive 2001/20/EC of the European Parliament and Council, which was transposed into legislation in the United Kingdom by the Medicines for Human Use (Clinical Trials) Regulations. Due to the emergency nature of the trial, it was not possible to obtain consent before enrolment. In accordance with the clinical trial regulations, and with permission from the ethics committee, consent to continue was sought after the initial emergency had passed.

In brief, PARAMEDIC-2 was a multicentre double-blinded placebo-controlled trial conducted by five National Health Service ambulance services in the United Kingdom from December 2014 to October 2017. Adult patients treated for OHCA who were not successfully resuscitated by means of defibrillation or CPR, and who met predetermined eligibility criteria, were randomly allocated to receive parenteral adrenaline or saline placebo. Randomisation occurred when trial paramedics opened packs containing prefilled 10 ml syringes loaded with either ten 1 mg doses of adrenaline or ten doses of 0.9% saline. Trial packs and their contents were identical in appearance and carried a unique identification number. In all other respects identical paramedic resuscitation protocols were followed [13].

Randomisation of drug packs to ambulance services was achieved using the minimisation method with an allocation ratio of 1:1. Patients, paramedics and trial staff were blinded to treatment allocation. The time of drug administration was entered manually in the ambulance clinical record.

Patients and the public were involved during the conception, design, conduct, interpretation and dissemination stages of the trial. Involvement was integrated through patient and public membership of the core research team and Trial Steering Committee, public consultation meetings and regular meetings with a patient and public advisory group.

Statistical analysis

Examining the influence of time to treatment was an a priori, planned analysis of the PARAMEDIC2 trial.

The time interval to administration of treatment was recorded from the time the first 999 emergency call was received to administration of the trial drug. Analyses assessed the primary outcome: survival at 30 days, and secondary outcomes: survival at discharge, ROSC at hospital admission and neurological outcome at discharge from hospital. The neurological outcome was measured using a modified Rankin scale (mRS) assessment [ranging from 0 (no symptoms) to 6 (death)] where a score of 0–3 inclusive was considered favourable [14].

The effect of time to administration of trial drug on primary and secondary outcomes was examined within the group of patients whose cardiac arrest was EMS or bystander witnessed. Analysis was restricted to these patients because the delay between cardiac arrest and the 999 call was unknown for unwitnessed cases. Some of the witnessed patients ($n=42$) were found to have a treatment time interval in excess of 60 min. Sensitivity analyses were performed to assess the influence of these extreme outliers.

All statistical analyses were undertaken using Stata, version 15.1 SE.

Baseline characteristics were summarised using mean, (standard deviation) or median and inter-quartile range for continuous data and number of patients (with percentages) for categorical data.

Logistic regression models were fitted for each of the four outcomes. For the unadjusted analyses, continuous time to administration of trial drug and the allocated treatment were modelled as explanatory factors. An interaction of these variables was fitted to model the effect of time on the estimated treatment effects. The adjusted analyses were corrected for pre-specified covariates [12] which included age, gender, aetiology (medical, traumatic, drowning, drug overdose, electrocution, asphyxial), initial rhythm (VF, pulseless VT, AED shockable, asystole, PEA/EMD, bradycardia, AED non-shockable), witness type (EMS, bystander) and bystander CPR (yes, no). For the adjusted models, initially, multivariable fractional polynomial models were fitted to determine best fit of model, as there was no reason to assume a constant proportional change in the odds ratio over time. Three transformations of the time variable were assessed: linear, first and second degree power transformations (e.g. time, time^a and time^a + time^b, respectively, where a and b are powers). Model fits were compared using Akaike information criterion (AIC). The smallest AIC indicated the best fit model. In the case of the linear model being the best fit model, the treatment effects over time were further assessed using logistic regression. The risk difference represents the difference averaged over time in the incidence of the outcome between the two interventions (having adjusted out the effect of the important covariates).

In a post-hoc analysis, the models were replicated separately for shockable and non-shockable sub-groups.

Role of the funding source

The trial was funded by the Heath Technology Assessment (HTA) Programme of the National Institute for Health Research (NIHR) (12/127/126). The funders had no role in the trial design, data collection or analysis, or in the writing of this report. The Warwick Clinical Trials Unit undertook data management activities. The trial statisticians assume responsibility for the integrity of the data and its analysis. The Current Controlled Trials number is ISRCTN73485024.

Results

Of 8014 patients enrolled in the study (3999 to placebo and 4015 to adrenaline), removal of unwitnessed cases and where the status of witness was unknown, reduced the numbers to 2437 (60.9%) and 2465 (61.4%), respectively. A further 50 patients with missing treatment time (23 from placebo and 27 from the adrenaline arm) were excluded. A CONSORT diagram demonstrates the rates of follow-up according to outcome (Fig. 1).

Baseline characteristics were summarised for the witnessed patients with treatment delay $\leq$ 60 min and are shown in Table 1. The interval between 999 emergency call and treatment administration were similarly distributed in both groups (Fig. 2).

The results of the multivariable fractional polynomial indicated that the linear fit was the most appropriate to the data for all outcomes.

Return of spontaneous circulation

Using the logistic regression model, it was estimated that when the trial drug was administered immediately after cardiac arrest (i.e. at time = 0) the odds of ROSC for those receiving adrenaline was more than twice that of patients given placebo (OR: 2.11, 95% CI 1.40–3.18, $p<0.001$.) The risk difference (RD) between treatment arms was estimated at 0.177 (95% CI 0.155–0.198, $p<0.001$).

The odds of ROSC (as opposed to no ROSC) at hospital admission decreased at a greater rate in the placebo arm compared with the adrenaline arm—in the placebo group by 0.93 (95% CI 0.92–0.95, $p<0.001$) for every unit increase in time (min) and by 0.96 (95% CI 0.95–0.97, $p<0.001$) in the adrenaline group. As timing of drug administration increases, the odds ratio of ROSC increases between the adrenaline and placebo groups by a factor of 1.03 for every additional minute (OR: 1.03, 95% CI 1.01–1.05, $p=0.005$).

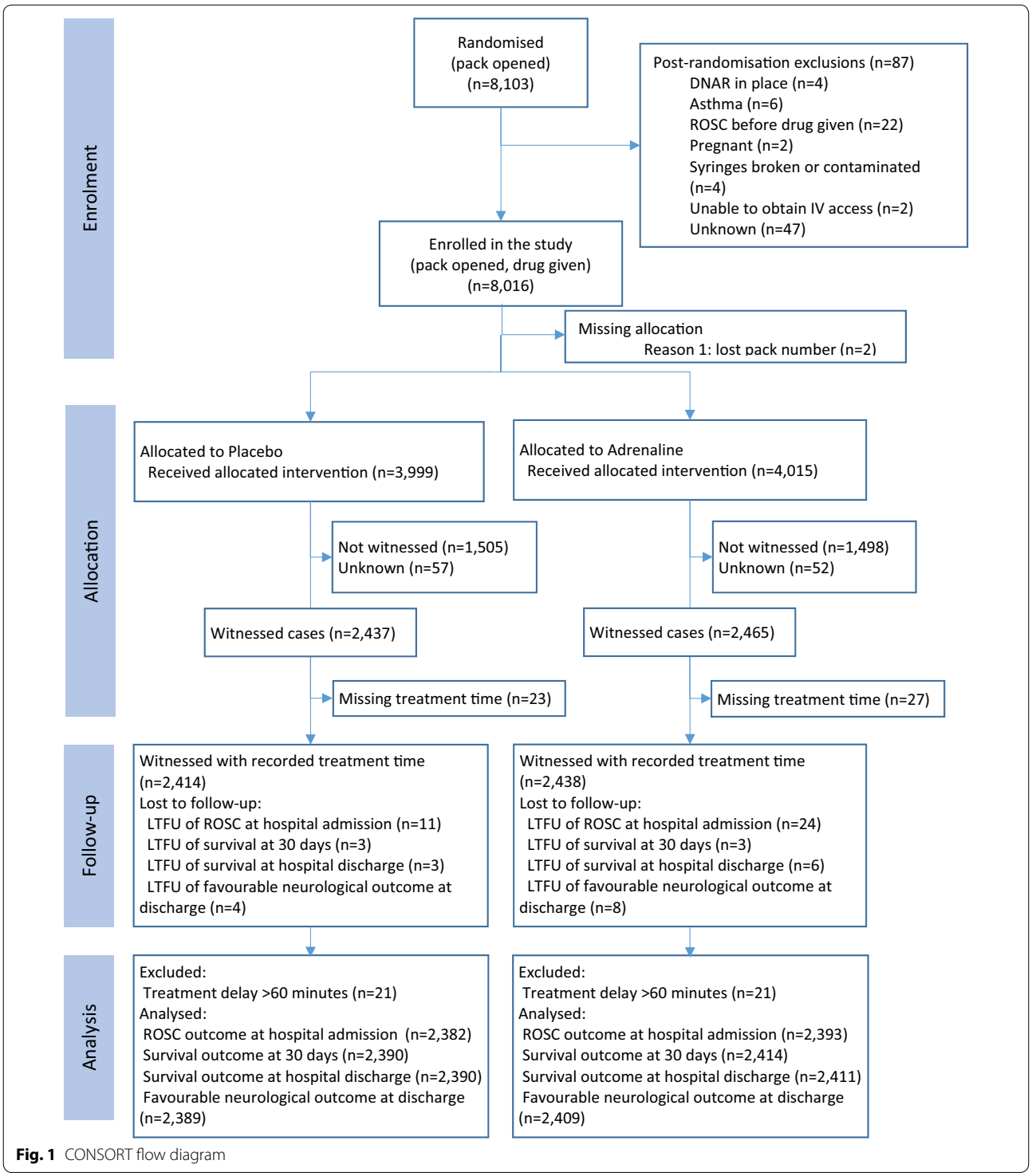


Fig. 1 CONSORT flow diagram

Figure 3 displays these results as probability of ROSC over time. For those given adrenaline immediately after cardiac arrest the probability of ROSC is 0.46 (95% CI 0.40–0.52) compared to 0.30 (95% CI 0.23–0.37) for those given placebo. After a delay in treatment of 40 min the probability reduces to 0.16 (95% CI 0.13–0.19) and 0.03 (95% CI 0.02–0.04), respectively.

Table 1 Patient characteristics by treatment arm for witnessed cases only ($n=4810$)

	Placebo ($n=2393$)	Adrenaline ($n=2417$)	Overall ($n=4810$)
Age (years)			
Mean (SD)	70.94 (15.26)	71.07 (15.3)	71[a] (15.28)
Median (IQR)	73.57 (21.10)	73.48 (21.45)	73.5[a] (21.28)
Time to treatment (min)			
Mean (SD)	21.73 (9.73)	21.72 (9.48)	21.73 (9.6)
Median (IQR)	20.93 (11.83)	21.08 (11.64)	21.00 (11.75)
Gender			
Male	1548 (64.69%)	1556 (64.38%)	3104 (64.53%)
Female	845 (35.31%)	861 (35.62%)	1706 (35.47%)
Initial rhythm			
Shockable	595 (24.86%)	604 (24.99%)	1199 (24.93%)
Of which:			
VF	542 (91.09%)	563 (93.21%)	1105 (92.16%)
Pulseless VT	19 (3.19%)	20 (3.31%)	39 (3.25%)
AED shockable	34 (5.71%)	21 (3.48%)	55 (4.59%)
Non-shockable	1765 (73.76%)	1763 (72.94%)	3528 (73.35%)
Of which:			
Asystole	1045 (59.21%)	1,000 (56.72%)	2045 (57.96%)
PEA/EMD	686 (38.87%)	724 (41.07%)	1410 (39.97%)
Bradycardia	14 (0.79%)	20 (1.13%)	34 (0.96%)
AED non-shockable	20 (1.13%)	19 (1.08%)	39 (1.11%)
Unknown	33 (1.38%)	50 (2.07%)	83 (1.73%)
Aetiology			
Medical (presumed cardiac)	2273 (94.99%)	2297 (95.04%)	4570 (95.01%)
Traumatic cause	36 (1.5%)	40 (1.65%)	76 (1.58%)
Drowning	0 (0%)	3 (0.12%)	3 (0.06%)
Drug overdose	24 (1%)	22 (0.91%)	46 (0.96%)
Electrocution	1 (0.04%)	0 (0%)	1 (0.02%)
Asphyxial	32 (1.34%)	28 (1.16%)	60 (1.25%)
Unknown	27 (1.13%)	27 (1.12%)	54 (1.12%)
Witnessed by			
EMS witnessed	452 (18.89%)	438 (18.12%)	890 (18.5%)
Bystander witnessed	1941 (81.11%)	1979 (81.88%)	3920 (81.5%)
Bystander CPR			
Yes	1353 (56.54%)	1386 (57.34%)	2739 (56.94%)
No[b]	1012 (42.29%)	1000 (41.37%)	2012 (41.83%)
Unknown	28 (1.17%)	31 (1.28%)	59 (1.23%)

[a] $n=3$ patients had no recorded age

[b] Includes EMS witnessed cases

Survival to 30 days and hospital discharge

The rate of survival to 30 days decreased as time to treatment increased in both the placebo and adrenaline group (odds: 0.92, 95% CI 0.89–0.95, $p<0.001$ and 0.9, 0.88–0.93, $p<0.001$, respectively).

The continuous covariate logistic model, suggests that the odds ratio of surviving to 30 days in the adrenaline arm (as opposed to placebo) did not change relative to placebo in relation to the time of drug administration ($p=0.41$. risk difference: 0.009, 95% CI − 0.002 to 0.019, $p=0.103$). The curves appear to converge after approximately 30 min from the time of cardiac arrest. However, these results include few cases at the two extremes of the time band and, therefore, have to be interpreted with caution. A similar pattern of results was noted for survival to hospital discharge (risk difference: 0.008, 95% CI − 0.002 to 0.019, $p=0.122$).

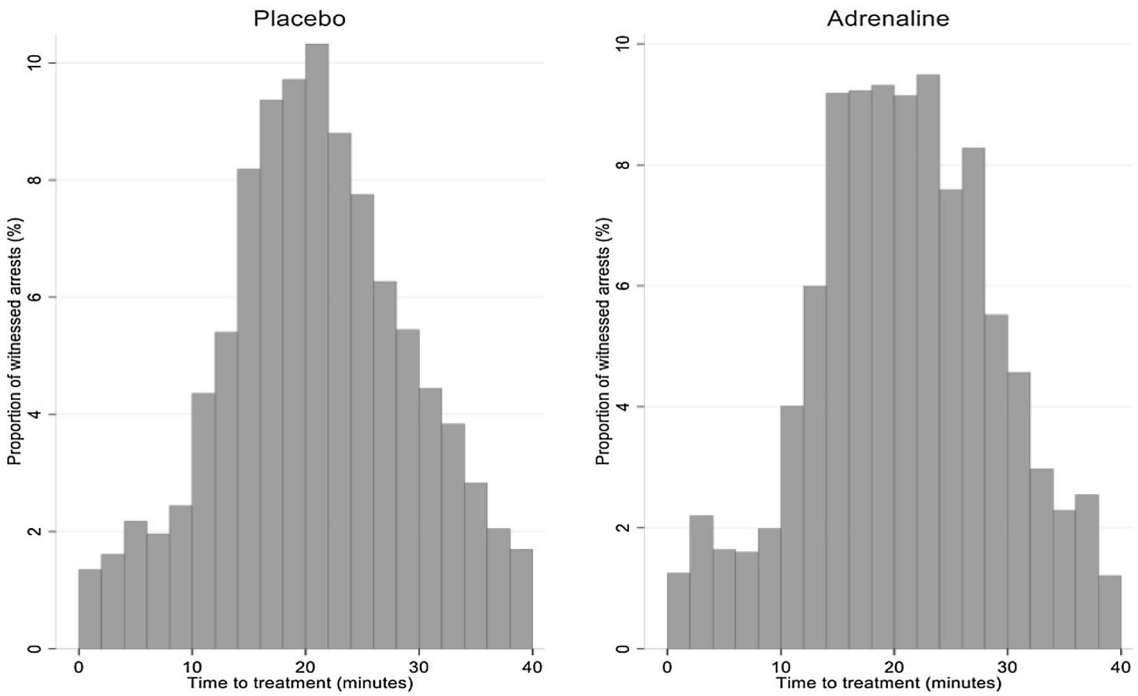


Fig. 2 Distribution of time to treatment by treatment type

The probability of survival had the trial drug been administered immediately after cardiac arrest is estimated to be 0.17 (95% CI 0.11–0.23) in the adrenaline group and 0.12 (95% CI 0.07–0.18) in the placebo group. When time from 999 call to treatment is 40 min the estimated probability of survival in both groups drops to < 0.01 (see Fig. 3).

Favourable neurological outcome at discharge

The proportion of patients who survived to hospital discharge with a favourable neurological outcome decreased with time in both the adrenaline and the placebo group ($p < 0.001$).

The odds ratio for favourable neurological outcome in the logistic model did not change over time ($p = 0.39$. risk difference: 0.004, 95% CI − 0.006 to 0.013, $p = 0.450$). The curves appear to converge after approximately 20 min from the time of cardiac arrest. This is limited by very low frequency counts and, therefore, should be interpreted with caution.

Figure 3 shows that the probability of survival with favourable neurological outcome is estimated to be 0.16 (adrenaline, 95% CI 0.09–0.22) and 0.12 (placebo, 95% CI 0.06–0.17) when time to treatment is zero minutes and < 0.01 for both groups when time to treatment is 40 min.

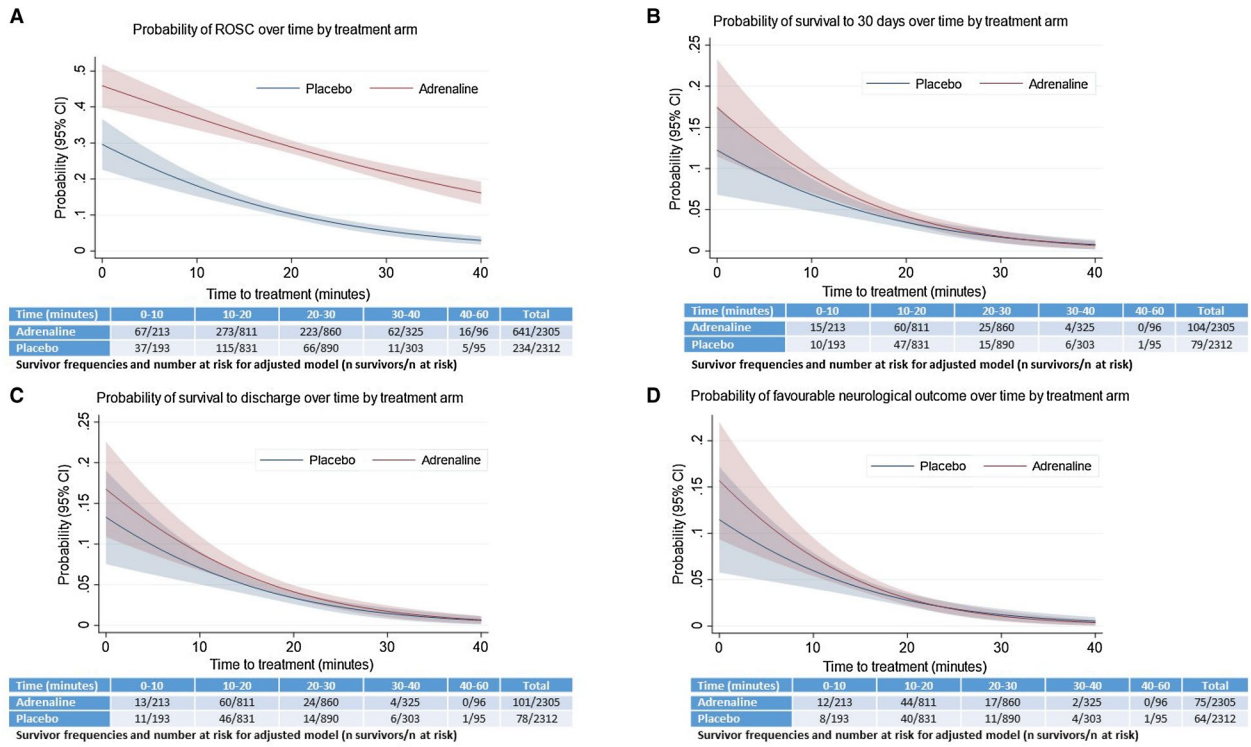
Initial rhythm

Results of separate analyses of patients with shockable and non-shockable rhythms (see electronic supplemental material) were very similar to the overall witnessed group, with the exception of patients with an initial shockable rhythm for ROSC at hospital admission, where the curves for difference in rate of ROSC overlapped during the first ten minutes of cardiac arrest (Fig. 4). The risk difference for those with shockable rhythms was 0.131 (95% CI 0.080–0.182, $p < 0.001$) and for non-shockable rhythms the risk difference was 0.192 (95% CI 0.169–0.215, $p < 0.001$). However, these results have to be interpreted with caution, due to the small number of patients within some of the time categories.

Sensitivity analyses and model selection

Sensitivity analysis showed that the removal of 42 patients with time to treatment in excess of 60 min (21 each arm) did not impact upon the conclusions of the analysis, therefore, the data were truncated at 60 min to maintain clinical plausibility and all results presented are based on these data.

Comparison of models with linear and non-linear time covariates identified that linear models offered the best fit for all four outcome variables. The results of model selection can be found in the electronic supplementary material.



Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	67/213	273/811	223/860	62/325	16/96	641/2305
Placebo	37/193	115/831	66/890	11/303	5/95	234/2312

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	15/213	60/811	25/860	4/325	0/96	104/2305
Placebo	10/193	47/831	15/890	6/303	1/95	79/2312

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	13/213	60/811	24/860	4/325	0/96	101/2305
Placebo	11/193	46/831	14/890	6/303	1/95	78/2312

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	12/213	44/811	17/860	2/325	0/96	75/2305
Placebo	8/193	40/831	11/890	4/303	1/95	64/2312

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Fig. 3 **a** Adjusted probability (95% CI) of ROSC over time by treatment arm. Model adjusted for age, gender, rhythm, aetiology, witness type and bystander CPR. Treatment OR ($t=0$): 2.11, 95% CI 1.40–3.18, $p<0.001$. Interaction OR: 1.03, 95% CI 1.01–1.05, $p=0.005$. **b** Adjusted probability (95% CI) of survival to 30 days over time by treatment arm. Model adjusted for age, gender, rhythm, aetiology, witness type and bystander CPR. Treatment OR ($t=0$): 1.78, 95% CI 0.79–4.00, $p=0.16$. Interaction OR: 0.98, 95% CI 0.94–1.03, $p=0.41$. **c** Adjusted probability (95% CI) of survival to hospital discharge over time by treatment arm. Model adjusted for age, gender, rhythm, aetiology, witness type and bystander CPR. Treatment OR ($t=0$): 1.46, 95% CI 0.654–3.30, $p=0.36$. Interaction OR: 0.99, 95% CI 0.95–1.04, $p=0.75$. **d** Adjusted probability (95% CI) of favourable neurological outcome at discharge over time by treatment arm. Model adjusted for age, gender, rhythm, aetiology, witness type and bystander CPR. Treatment OR ($t=0$): 1.65, 95% CI 0.66–4.11, $p=0.28$. Interaction OR: 0.98, 95% CI 0.93–1.03, $p=0.39$

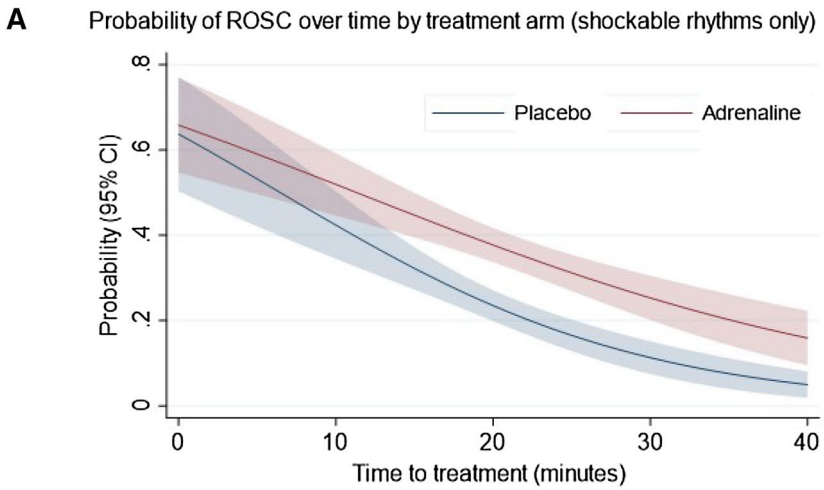
Unadjusted analyses yielded similar results to the reported adjusted analyses (electronic supplementary material).

Discussion

The main findings of this study are that the rates of ROSC on arrival at hospital, survival and favourable neurological outcome all decreased as the interval from cardiac arrest to the administration of drug or placebo increased. The best outcomes are seen early after the onset of cardiac arrest. Models of time to drug administration showed a pattern which suggests that the relative effects of adrenaline to placebo on ROSC increased over time, although the absolute difference remained fairly consistent over time. By contrast, the effects of adrenaline relative to placebo on survival and favourable neurological outcomes did not change over time.

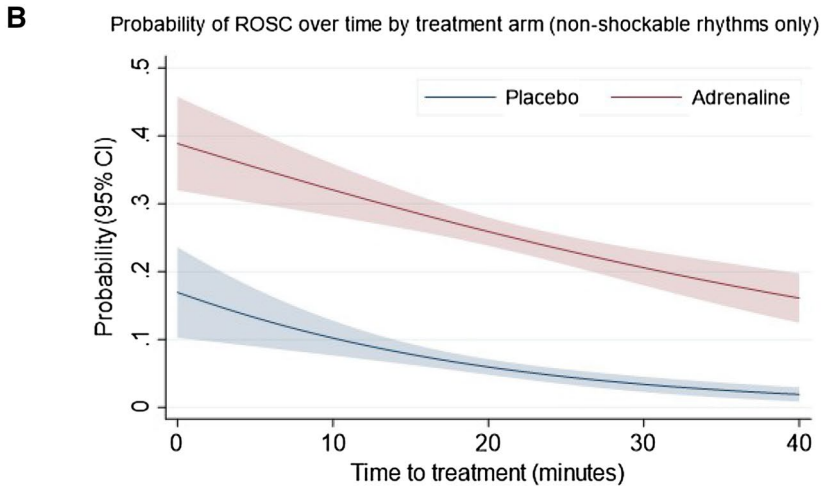
The observation that ROSC, survival and neurological outcomes deteriorate the longer a patient is in cardiac arrest is consistent with previous studies [15–18]. This underlies the phenomenon known as resuscitation time bias, whereby interventions given early after the onset of cardiac arrest appear to be beneficial relative to late interventions, but the better outcomes are in fact related to earlier treatment [11, 19]. The randomised design of the PARAMEDIC2 study removes the influence of resuscitation time bias, allowing an unbiased assessment of changes in treatment effect over time. The study reaffirms that during cardiac arrest, any traditional time-to intervention analyses are likely to be severely biased. It highlights the importance of more sophisticated statistical analyses of observational data which can partly deal with this problem [11, 20].

The novel finding that the effects of adrenaline on ROSC compared with placebo increase over time are consistent with experimental studies. In a rat model of cardiac arrest Angelos et al. found no difference between placebo and adrenaline in the rate of ROSC in cardiac arrests of very short duration (less than 2 min) [21]. As the duration of cardiac arrest increased,



Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	16/37	102/239	74/211	16/72	2/20	210/579
Placebo	16/32	76/235	32/238	6/65	2/17	132/587

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)



Time (minutes)	0-10	10-20	20-30	30-40	40-60	Total
Adrenaline	51/176	171/572	149/649	46/253	14/76	431/1726
Placebo	21/161	39/596	34/652	5/238	3/78	102/1725

Survivor frequencies and number at risk for adjusted model (n survivors/n at risk)

Fig. 4 **a** Adjusted probability (95% CI) of ROSC over time by treatment arm (shockable rhythms only). Model adjusted for age, gender, rhythm, aetiology, witness type and bystander CPR. Treatment OR ($t=0$): 1.10, 95% CI 0.52–2.32, $p=0.81$. Interaction OR: 1.03, 95% CI 0.99–1.07, $p=0.10$. **b** Adjusted probability (95% CI) of ROSC over time by treatment arm (non-shockable rhythms only). Model adjusted for age, gender, rhythm, aetiology, witness type and bystander CPR. Treatment OR ($t=0$): 3.22, 95% CI 1.90–5.47, $p<0.001$. Interaction OR: 1.03, 95% CI 1.00–1.06, $p=0.03$

adrenaline played an increasingly important role in restoring ROSC. These findings are consistent with the 3-phase cardiac arrest model described by Weisfeldt and Becker which reflects the time sensitive changes in metabolic and physiological profiles the longer the duration of a cardiac arrest. In this model, vasopressors are recommended during the later circulatory and metabolic phases (>4 min) [22]. At a cellular level this can be explained as within minutes of the onset of cardiac arrest, myocardial adenosine triphosphate levels

decrease, leading to the disruption of normal myocardial cellular homeostasis [6]. Unlike the heart, the brain is more sensitive to tissue ischaemia as it has no myoglobin oxygen stores [23, 24]. Furthermore, CPR and vasopressors may be less effective at restoring mitochondrial function in the brain than it is at restoring cardiac mitochondrial performance [25].

A key unanswered question in PARAMEDIC2 was the influence of time to drug administration. The time from collapse to drug treatment was on average 22 min. This is longer than the interval during in-hospital cardiac arrest (average 3 min) [9, 10] and during the majority of animal cardiac arrest models (average 9.5 min) [26]. The timing is similar to a systematic review of time to drug administration across 17 studies [19.4 min (95% CI 12.8–25.9)] [27] and with more recent studies (range 13–24 min) [28–31]. This analysis of time to treatment shows that the shorter the time to treatment, whether treatment was adrenaline or placebo, is associated with the best outcomes. Current treatment algorithms recommend that CPR is started (and if indicated defibrillation) before adrenaline is administered. This finding is, therefore, probably related to a shorter duration of low or no flow time after the onset of cardiac arrest. The later administration of adrenaline increases the chances of ROSC relative to placebo but without incremental improvement in longer term outcomes. This discordance may in part explain improved ROSC, but smaller effects on long-term survival and minimal influence on favourable neurological outcome.

The present study explored if the treatment effects differed according to whether the initial rhythm was shockable or non-shockable. In an analysis of in-hospital cardiac arrests with an initial shockable rhythm, Andersen et al. found that very early (within 2 min of first defibrillation) compared with no or late adrenaline (> 2 min) was associated with lower rates of ROSC (OR 0.71, 95% CI 0.60–0.83), survival (OR 0.70, 95% CI 0.59–0.82) and survival with a favourable neurological outcome (OR 0.69, 95% CI 0.58–0.83) [9]. In OHCA (time to drug administration 13 min), Ewy et al. found that delayed adrenaline reduced survival (aOR 0.94, 95% CI 0.91–0.97) in patients with shockable rhythms but did not affect neurological outcomes. Hayashi noted both improved survival and better neurological outcomes in those who received adrenaline within 10 min of cardiac arrest [32]. The present study suggests that very early adrenaline does not increase the rates of ROSC in patients with an initially shockable rhythm.

Overall outcomes are worse where the initial rhythm is non-shockable. During in-hospital cardiac arrest, Donnino et al. noted a stepwise reduction in survival and favourable neurological outcome with delays in adrenaline administration exceeding 1–3 min [10]. In OHCA, Hansen et al. found that every minute delay to the administration of adrenaline decreased survival (OR 0.96, 95% CI 0.95–0.98) and favourable neurological outcomes (OR 0.94, 95% CI 0.89–0.98) [33]. By contrast, the present study was consistent with Ewy et al. in finding no difference in longer term outcomes according to the time of adrenaline administration for patients with non-shockable rhythms [29].

Compared with observational studies, the randomised double-blind design of this trial reduced the influence of confounding (due to patient characteristics and resuscitation time bias), performance and ascertainment bias. The pragmatic nature of the trial, embedded within National Health Service Ambulance Services, increased generalisability to similar settings. Although defined a priori, analysis of time to drug administration was not the primary intent of the PARAMEDIC2 study. As such, the results should be considered exploratory and interpreted with caution. The study pooled EMS-witnessed and bystander witnessed cardiac arrests as there were insufficient numbers to analyse separately. For the sub-group analysis according to rhythm, patients were analysed in groups according to their initial presenting rhythm. This does not account for any subsequent rhythm transitions. The relatively few patients with an initial shockable mean the findings need to be interpreted cautiously. Post-resuscitation care treatments (targeted temperature management, haemodynamic and ventilator management, percutaneous coronary intervention, prognostication) were recommended but were not strictly protocolised or monitored. It is possible that different approaches to post-resuscitation care may have influenced longer term outcomes. Alternative dosing regimens such as higher or lower doses, use of a continuous infusion, may have produced different results. Finally, the findings of worse outcomes overall with later interventions should be considered when designing and estimating sample sizes in future trials.

In conclusion, rate of ROSC, survival and favourable neurological outcomes reduce the longer the duration of cardiac arrest. This confirms that early treatment of cardiac arrest rather than specifically the administration of adrenaline, provides the best outcomes. As time progresses, the effects of adrenaline on the rate of ROSC increase relative to placebo. By contrast, the rate of survival and favourable neurological outcomes was not substantively different over time between the adrenaline and placebo groups.

Electronic supplementary material
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Author contributions
GDP, CK, CJ, CD, JN, TQ, JF, SG and RL conceived the study, RF, IG, HP, NR, LO contributed to the acquisition of the data. CK, CJ, RL analysed the data with input from SG. GDP, CK, CJ and RL drafted the work. All authors revised it for important intellectual content and approved the version to be published. CK, CJ, RL had full access to all the data in the study. All authors shared the final responsibility for the decision to submit for publication. GDP acts as guarantor.

Ethical approval
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Oxford C REC: 14/SC/0157) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflicts of interest
All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: support from the NIHR for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; GDP, CD, JN, JF have volunteer roles with the International Liaison Committee on Resuscitation, European (GDP, JN), UK (GDP, JN, CD) and Australian (JF) Resuscitation Councils.

Data sharing
Requests for access to data from the study should be addressed to the corresponding author at paramedic@warwick.ac.uk. The study protocol has been published. All proposals requesting data access will need to specify how it is planned to use the data, and all proposals will need approval of the trial co-investigator team.

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