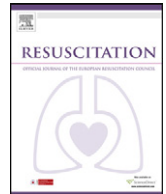




Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation



Clinical paper

Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial[☆]

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ARTICLE INFO

Article history:

Received 19 June 2011

Received in revised form 22 June 2011

Accepted 24 June 2011

Available online xxx

Keywords:

Adrenaline

Out of hospital cardiac arrest

Randomised controlled trial

Survival

Ambulance

ABSTRACT

Background: There is little evidence from clinical trials that the use of adrenaline (epinephrine) in treating cardiac arrest improves survival, despite adrenaline being considered standard of care for many decades. The aim of our study was to determine the effect of adrenaline on patient survival to hospital discharge in out of hospital cardiac arrest.

Methods: We conducted a double blind randomised placebo-controlled trial of adrenaline in out-of-hospital cardiac arrest. Identical study vials containing either adrenaline 1:1000 or placebo (sodium chloride 0.9%) were prepared. Patients were randomly allocated to receive 1 ml aliquots of the trial drug according to current advanced life support guidelines. Outcomes assessed included survival to hospital discharge (primary outcome), pre-hospital return of spontaneous circulation (ROSC) and neurological outcome (Cerebral Performance Category Score – CPC).

Results: A total of 4103 cardiac arrests were screened during the study period of which 601 underwent randomisation. Documentation was available for a total of 534 patients: 262 in the placebo group and 272 in the adrenaline group. Groups were well matched for baseline characteristics including age, gender and receiving bystander CPR. ROSC occurred in 22 (8.4%) of patients receiving placebo and 64 (23.5%) who received adrenaline (OR = 3.4; 95% CI 2.0–5.6). Survival to hospital discharge occurred in 5 (1.9%) and 11 (4.0%) patients receiving placebo or adrenaline respectively (OR = 2.2; 95% CI 0.7–6.3). All but two patients (both in the adrenaline group) had a CPC score of 1–2.

Conclusion: Patients receiving adrenaline during cardiac arrest had no statistically significant improvement in the primary outcome of survival to hospital discharge although there was a significantly improved likelihood of achieving ROSC.

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1. Introduction

Cardiac arrest occurring out of hospital is a significant public health issue with an estimated incidence in the United States of 95.7 per 100,000 person years.^{1,2} The overall case fatality varies across different emergency medical services, but is mostly in excess of 90% and has improved little over the last three decades.² The routine use of adrenaline (epinephrine) in treating cardiac

arrest has been recommended for over half a century, being first described in 1906.³ The International Liaison Committee on Resuscitation (ILCOR) include adrenaline in their advanced life support (ALS) resuscitation guidelines, despite there being no randomised placebo-controlled trials in humans evaluating its efficacy in cardiac arrest.⁴ In 2010 ILCOR identified the need for randomised clinical trials of vasopressor drugs in the treatment of cardiac arrest.⁴

Animal studies have shown that adrenaline improves coronary and cerebral perfusion.⁵ The survival outcomes in human studies (non randomised and observational) have been equivocal.^{6–9} A meta-analysis of high dose versus standard dose adrenaline did not include a comparison with no adrenaline and showed some benefit of high dose adrenaline on return of spontaneous circulation (ROSC) but not survival to hospital discharge.¹⁰ In contrast, there has been some concern regarding the potential harmful effects of

[☆] A Spanish translated version of the abstract of this article appears as Appendix in the final online version at doi:10.1016/j.resuscitation.2011.06.029.

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adrenaline on post cardiac arrest myocardial function and cerebral microcirculation.^{11,12}

Despite adrenaline being universally considered “standard of care” in the treatment of cardiac arrest there has never been a randomised placebo-controlled trial to establish its efficacy. This study, the first randomised placebo-controlled clinical trial of adrenaline in cardiac arrest, was undertaken to address this knowledge deficit.

2. Methods

2.1. Study patients and setting

The study was undertaken in Western Australia (WA), an area covering 2.5 million km² with a population of 1.96 million. Approximately 12% of the population are aged over 64 years and 73% of the population reside in the capital city of Perth.¹³ WA is served by a single emergency ambulance service provided under government contract by St John Ambulance Western Australia (SJA-WA). All calls for ambulances throughout WA are received centrally and ambulances dispatched by the ambulance service communication centre located in Perth. All ambulances in Perth and larger regional centres in WA are staffed by career paramedics where their scope of clinical care is governed by specific SJA-WA clinical practice guidelines. The management of cardiac arrest is based on the recommendations of the Australian Resuscitation Council (ARC).¹⁴ During the study period this included defibrillation with a manual defibrillator and securing the airway with either a tracheal tube or laryngeal mask airway, however no drugs were administered. This long standing policy on no drug administration had been adopted by SJA-WA in recognition of the lack of any evidence for improved survival and the potential to adversely affect other resuscitation interventions, in particular uninterrupted chest compressions. The policy enabled the introduction of this single stand-alone drug intervention (adrenaline versus placebo) in the context of a randomised controlled trial.

2.2. Study design

We conducted a randomised double blind placebo-controlled trial (RCT) in out-of-hospital cardiac arrest patients attended by SJA-WA paramedics. Patients in cardiac arrest were randomised to receive either intravenous preparations of adrenaline 1:1000 or placebo (sodium chloride 0.9%).

2.3. Study outcomes

The primary endpoint was survival to hospital discharge with secondary endpoints of pre-hospital return of spontaneous circulation (ROSC) (defined as a period of sustained ROSC in the field for greater 30 s) and Cerebral Performance Category (CPC) at hospital discharge. CPC scores are defined as: I – normal function, II – mild to moderate disability, III – severe disability, IV – vegetative state, and V – dead.^{15,16}

2.4. Study approvals

The study was approved by the Human Research Ethics Committee of the University of Western Australia (No. RA/4/1/0524) and waiver of consent was granted. The study was registered with the Australian and New Zealand Clinical Trials Register (ACTRN12605000062628).

2.5. Study procedures

All out-of-hospital cardiac arrests attended by SJA-WA paramedics between 11th August 2006 and 30th November 2009

were screened for entry into the trial. Patients suffering a cardiac arrest from any cause, aged 18 years or older with resuscitation commenced by paramedics were eligible for entry. Resuscitation was undertaken in accordance with existing SJA-WA guidelines which were consistent with the recommendations of the ARC, namely that 1 ml of adrenaline 1:1000 (i.e. 1 mg) be administered every 3 min.¹⁴ Randomisation occurred at the time that it became evident that the administration of IV adrenaline was indicated, and was actioned by selection of the study drug ampoule. As per the resuscitation protocol at the time this occurred after the third unsuccessful shock or after the establishment of IV access in the case of non-shockable cardiac arrest rhythms. As such, those who responded early to defibrillation were not randomised.

Study drugs were commercially prepared in identical 10 ml vials with tamperproof seals distinguishable only by a specific randomisation number. The drugs were prepared independent of the investigators and numbered according to a computer generated randomisation schedule. The randomised study drugs were then centrally issued to paramedic crews using the same distribution process as for other drugs used within the ambulance service.

Each ambulance carried two 10 ml vials of the study drug and these were replaced from central stores as required. In both treatment arms aliquots of 1 ml of the study drug (1 mg adrenaline or 1 ml normal saline) were administered in conjunction with a free flowing intravenous infusion or 30 ml flush of normal saline. The study drug was administered as clinically indicated with a maximum dose of 10 ml (10 mg adrenaline or 10 ml normal saline). No other resuscitation drugs were administered pre-hospital during the trial and tracheal administration of drugs was not permitted. SJA-WA clinical protocol allowed for resuscitation efforts to be terminated in the field providing the patient remained in asystole after a minimum of 20 min of maximal resuscitation efforts. Where patients were subsequently transported to hospital the treating ED clinicians were unaware of drug assignment and managed the patient as per their usual clinical practice.

Prior to the commencement of the trial each paramedic completed training relevant to the study, as part of their routine SJA-WA two day continuing education program. Specifically this training included, pharmacology of adrenaline, familiarisation with the trial protocol, further practice in intravenous cannulation and cardiac arrest simulation exercises. Testing was undertaken at the completion of the training sessions to ensure the prerequisite resuscitation competency standard had been achieved. This training was provided to all paramedics regardless of their intention to participate in the study.

2.6. Data collection

Demographic and clinical information for all cardiac arrest patients attended by SJA-WA is manually recorded on a patient care record (PCR) by the paramedic at the completion of each event. The PCR is clinically reviewed and data manually entered into the SPSS statistical package. Each record is then subsequently linked to data received via the ambulance service computer aided dispatch (CAD) system. Together these data form the WA Ambulance Service Cardiac Arrest Registry extending from January 1996 onwards. The relevant information for each case is extracted from the state based Emergency, Hospital Morbidity and Mortality data systems to determine outcome. CPC scores are derived from medical chart review for patients surviving to hospital discharge, with the chart reviewer blinded to the study group allocation. Data elements and definitions were consistent with the Utstein definitions for reporting out of hospital cardiac arrest.¹⁶ For patients entered into the trial an additional single page case report form was used to collect data not routinely collected as part of the PCR, including randomisation number, total dose of adrenaline administered, whether

intravenous access was achieved and total volume of intravenous fluids infused.

2.7. Statistical analysis

The sample size required for the study was 2213 patients per group. This was derived on a baseline survival to hospital discharge of 5% with an absolute improvement in survival of 2%, alpha 0.05 (two tailed) and power of 80%. A total patient enrolment of 5000 was planned to account for losses to follow-up. Recruitment of the required sample was considered feasible as agreement had been reached with a number of other Australian and New Zealand ambulance services to participate in this trial. Unfortunately these ambulance services were subsequently unable to participate, resulting in this study becoming a single centre trial in WA.

Patient and study characteristics were described using proportions and means, with differences assessed using Pearson's chi-square and *t*-test (or Mann–Whitney) for categorical and continuous data respectively. Ambulance time intervals were described using means, medians and interquartile ranges (IQR). Odds ratios (OR) and 95% confidence intervals were derived for primary and secondary outcomes. Logistic regression was used to adjust for potential confounders on the treatment effect of the study drug. It was planned 'a priori' to conduct subgroup analysis of primary and secondary outcomes by shockable versus non-shockable initial cardiac arrest rhythm. Analysis was performed on an intention to treat basis and per protocol basis using SPSS statistical software version 17. All statistical tests were two sided with a significance level of 0.05.

3. Results

A total of 4103 out of hospital cardiac arrests were attended by the Ambulance Service during the study period. Of these 3502 were excluded from the study, including 2513 because resuscitation efforts were not commenced by paramedics as death had clearly been established. Of the 601 patients randomised, 67 were unable to be analysed due to randomisation number not being recorded, resulting in 262 and 272 in the placebo and adrenaline groups respectively (Fig. 1).

Overall mean age was 65 years and 73% were males. Most (>90%) of the arrests were deemed to be of cardiac aetiology, the initial cardiac arrest recorded by the paramedics was VF/VT in 46% of cases and 51% received bystander CPR. Patient and arrest characteristics were evenly distributed between placebo and adrenaline groups with the exception of more patients resuscitated to hospital in the adrenaline group (Table 1).

For patients administered adrenaline the likelihood of achieving ROSC pre-hospital was 3.4 times greater than for those receiving placebo (23.5% versus 8.4%; OR 3.4; 95% CI 2.0–5.6). (Table 2) Adrenaline was also associated with a significant increase in the proportion of patients admitted from the ED to hospital (25.4% versus 13.0%; OR 2.3; 95% CI 1.4–3.6). While more than twice the number of patients who received adrenaline survived to hospital discharge, this failed to reach statistical significance (4.0% versus 1.9%; OR 2.2; 95% CI 0.7–6.3). Good neurological outcome (CPC 1 or 2) was achieved in 14 out of the 16 survivors. The two unfavourable neurological outcomes (one CPC = 3 and one CPC = 4) occurred in the adrenaline group. The treatment effect of adrenaline on pre-hospital ROSC was more marked in non-shockable rhythms (OR 6.9; 95% CI 2.6–18.4) than shockable rhythms (OR 2.4; 95% CI 1.2–4.5), but in neither sub-group was there a significant effect on survival to hospital discharge (Table 3). Findings were essentially unchanged where a 'per protocol' analysis was undertaken for the 520 patients

(*n* = 256 placebo versus *n* = 264 adrenaline) who actually received the study drug.

Logistic regression modelling was undertaken to control for the effect of potential confounders on the relationship between study drug and patient outcome. The following factors were entered (concurrently) into the model based on univariate analysis and clinical rationale: patient age (in years), male gender, bystander witnessed, initial rhythm shockable, response interval (in minutes) and study drug. There was little change in the effect of adrenaline on ROSC (OR 3.5; 95% CI 2.1–6.0) or survival to hospital discharge (OR 2.1; 95% CI 0.7–6.3) in the fully adjusted models. The presence of an initial shockable rhythm was the only other factor associated with the likelihood of pre-hospital ROSC in the adjusted model (OR 1.9; 95% CI 1.1–3.1). Similarly an initial shockable rhythm (OR 9.5; 95% CI 2.0–45.3) was also associated with improved survival to hospital discharge, together with younger age (OR 0.96; 95% CI 0.93–0.99).

4. Discussion

This is the first randomised placebo-controlled trial of adrenaline in cardiac arrest. Our study demonstrated that adrenaline resulted in a statistically significant increase in ROSC (OR 3.4; 95% CI 2.0–5.6) but not in the primary outcome of survival to hospital discharge (OR 2.2; 95% CI 0.7–6.3). However, the only two survivors with a poor neurological outcome were in the adrenaline group. For both shockable and non-shockable initial cardiac arrest rhythms we observed significantly better outcomes in terms of ROSC and hospital admission with the use of adrenaline.

These findings are consistent with other observational studies and non-randomised trials, but there are no randomised trials in humans for direct comparison. In a RCT of intravenous drug administration versus no such intervention during cardiac arrest, Olasveengen et al. reported a doubling in the proportion of patients achieving ROSC (OR 1.99; 95% CI 1.48–2.67) and a non-significant increase in the proportion surviving to hospital discharge (OR 1.16; 95% CI 0.74–1.82).⁸ This study however is fundamentally different to ours in that the intervention under investigation was the establishment of intravenous access by paramedics and by default administration of drugs during resuscitation. In their study, for those randomised to intravenous access, 79% received adrenaline, 46% atropine and 17% amiodarone. From the data provided it was not possible to determine the clinical effects of these drugs, either individually or in combination, on the reported outcomes. Furthermore as the intervention could not be blinded, the potential for paramedics to respond differently, particularly knowing patients randomised to no intravenous access group would have drug therapy withheld, may have introduced a bias. While the investigators identified no difference in a number of CPR quality measures across both study arms in the 75% of events assessed, the potential bias inherent with non-blinding cannot be ruled out. What this study demonstrates is that the administration of resuscitation drugs during out of hospital cardiac arrest is associated with improvements in short term survival.

The findings of several non-randomised clinical trials designed to evaluate the efficacy of adrenaline in cardiac arrest have been equivocal.^{7,9} In a before and after evaluation of the introduction of adrenaline in the management of out of hospital cardiac arrest in Singapore, no improvement in the proportion of patients achieving ROSC was observed (OR 0.9; 95% CI 0.6–1.2). There was however a 70% (albeit non significant) improvement in those surviving to hospital discharge (OR 1.7; 95% CI 0.6–4.5)⁹. In this study only 40% of patients received adrenaline during the adrenaline phase and paramedics were only authorised to administer a single 1 mg dose of adrenaline. This dose is much less than the resuscitation guideline recommendations of adrenaline 1 mg given every 3–5 min.¹⁴

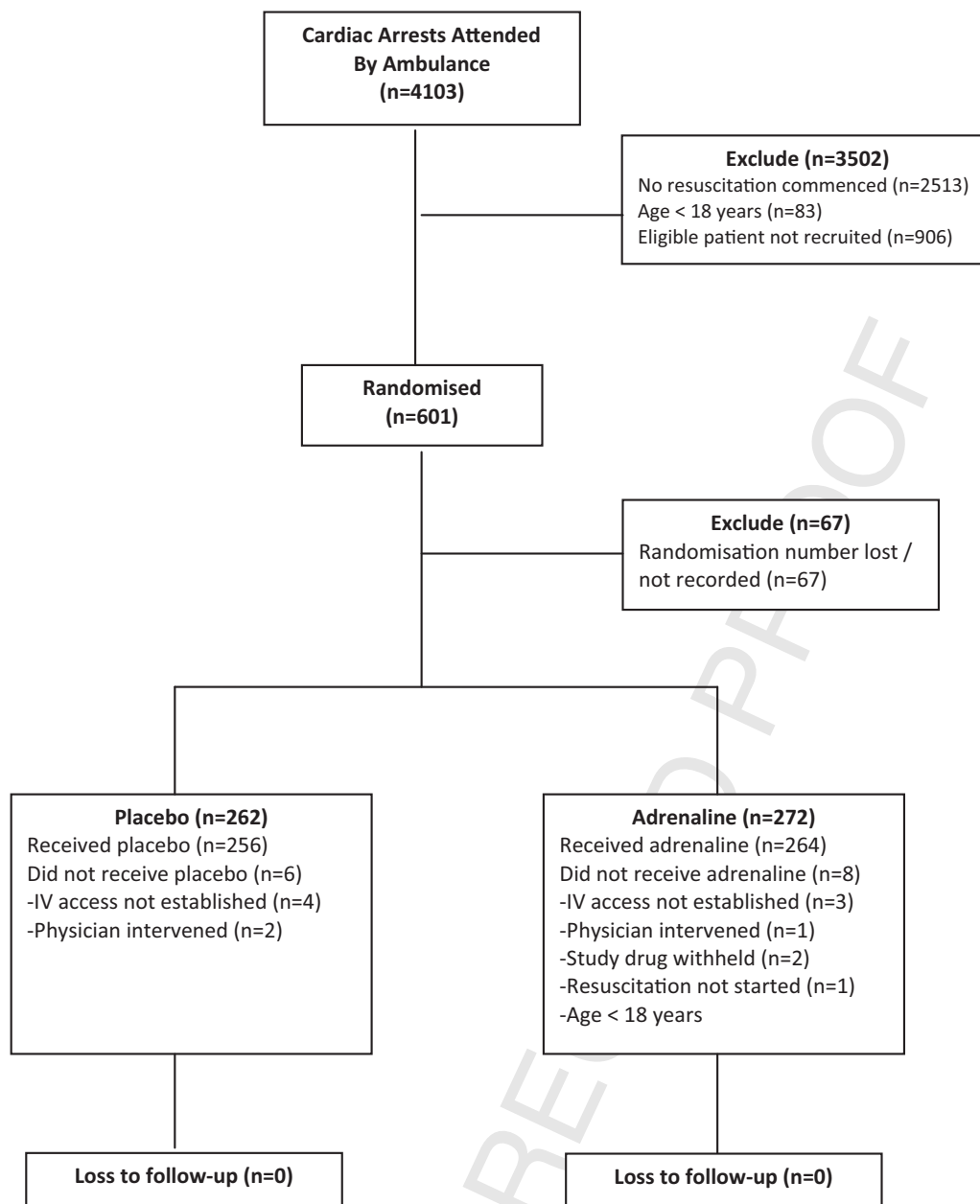


Fig. 1. Study profile.

Other observational studies have failed to demonstrate improved short or long term benefits of adrenaline in cardiac arrest.^{7,17}

The only other randomised trials of adrenaline in cardiac arrest have compared high dose versus standard dose of adrenaline, without reference to placebo or non-administration of adrenaline.¹⁸⁻²⁰ Without exception all these trials demonstrated the superiority of high dose adrenaline in achieving ROSC, however they also failed to demonstrate better outcomes in survival to hospital discharge. In a subsequent meta-analysis of high versus low dose adrenaline in cardiac arrest the pooled odds ratio for ROSC and survival to hospital discharge was 1.14 (95% CI 1.12-1.27) and 0.53 (95% CI 0.53-1.03) respectively, the latter even suggesting the possibility of adrenaline adversely impacting on survival.¹⁰

All the studies published to date have employed less robust study designs, used adrenaline doses much lower than recommended for cardiac arrest or compared larger doses of adrenaline against unproven standard dose adrenaline regimens. Accordingly these studies failed to address the fundamental question of the

efficacy of adrenaline in treating cardiac arrest. Our study clearly demonstrates the superiority of adrenaline over placebo in achieving ROSC. While not the primary outcome of our study, ROSC is an increasingly important clinical endpoint as the influence of post resuscitation care interventions (i.e.: therapeutic hypothermia, managing underlying cause, organ perfusion and oxygenation) on survival to hospital discharge are recognised.^{21,22} Our study demonstrated a doubling of survival to hospital discharge that did not reach statistical significance possibly because the study was underpowered for the primary endpoint.

While this was a double blind randomised placebo-controlled trial there were a number of limitations. Firstly we were unable to achieve full patient recruitment as planned. This study was designed as a multicentre trial involving five ambulance services in Australia and New Zealand and was accordingly powered to detect clinically important treatment effects. Despite having obtained approvals for the study from Institutional Ethics Committees, Crown Law and Guardianship Boards, the concerns of

Table 1
Demographic and patient characteristics by treatment arm.

Characteristic	Placebo (n = 262)	Adrenaline (n = 272)	p-Value
Age in years: mean (SD)	64.9 (17.4)	64.3 (17.5)	0.69
Male, n (%)	196 (74.8)	193 (71.0)	0.33
Location of arrest: n (%)			
Home	181 (69.1)	204 (75.0)	0.25
Public place	69 (26.3)	55 (20.2)	
Other	12 (4.6)	13 (4.8)	
Cardiac aetiology: n (%)	242 (92.4)	246 (90.4)	0.43
Cardiac arrest witnessed: n (%)			
Bystander	138 (52.7)	120 (44.1)	0.05
Paramedic	14 (5.3)	26 (9.6)	0.06
Bystander CPR, n (%)	129 (49.2)	144 (52.9)	0.39
Initial cardiac arrest rhythm: n (%)			
VF/VT	126 (48.1)	119 (43.8)	0.24
PEA	70 (26.7)	91 (33.5)	
Asystole	66 (25.2)	62 (22.8)	
Ambulance response interval (min): mean (SD)	10.2 (7.3)	10.1 (5.5)	0.76
Airway management: n (%)			
Tracheal intubation	198 (75.6)	192 (70.6)	0.19
Laryngeal mask airway	61 (23.3)	66 (24.3)	0.79
Volume of trial drug administered (ml): median (IQR)	5.0 (3.0–8.0)	5.0 (3.0–7.0)	0.13
Volume of IV fluids administered (ml): median (IQR)	500 (237–700)	500 (200–700)	0.28
Transported to hospital: n (%)	215 (82.1)	241 (88.6)	0.03

being involved in a trial in which the unproven “standard of care” was being withheld prevented four of the five ambulance services from participating. In addition adverse press reports questioning the ethics of conducting this trial, which subsequently led to the involvement of politicians, further heightened these concerns. Despite the clearly demonstrated existence of clinical equipoise for adrenaline in cardiac arrest it remained impossible to change the decision not to participate. As a single centre study with approximately 500 out of hospital cardiac arrests in which resuscitation is commenced per year, it would not have been possible to reach the required sample size. In addition it was not possible to continue as the study drugs reached their expiry date and no additional funding was available. The failure to achieve an adequate sample size left the trial underpowered to detect significant effects on survival to hospital discharge.

Second we were unable to assess the influence of CPR quality or the timing of adrenaline administration during resuscitation on our findings. However we considered this trial needed to be prag-

matic in having few exclusion criteria, recognising that the timing of drug administration will vary depending on the successful establishment of intravenous access and variations in the resuscitation processes of care including CPR quality. This, in essence reflects current clinical practice. As blinding was well preserved in this study we consider the likelihood of these factors being differentially distributed between the two study arms to be small.

Finally, participation in the study by the SJA-WA paramedics was voluntary, hence only 40% of eligible patients were recruited. We are unable to exclude the potential for selection bias, however trial patients were well matched on baseline characteristics and there is no reason to suggest that paramedics who participated in the trial were more likely to selectively enroll patients into the trial.

This study is unique in that it is the first randomised double blind placebo-controlled trial of adrenaline in cardiac arrest. To date the evidence base underpinning this “standard of care” intervention has been restricted to animal and non-randomised clinical studies that are characterised by inconsistent findings. The extensive bar-

Table 2
Outcomes for patients receiving placebo versus adrenaline.

Outcome	Placebo (n = 262), n (%)	Adrenaline (n = 272), n (%)	OR (95% CI)	p-Value
ROSC achieved pre-hospital	22 (8.4%)	64 (23.5%)	3.4 (2.0–5.6)	<0.001
Admitted to hospital	34 (13.0%)	69 (25.4%)	2.3 (1.4–3.6)	<0.001
Survived to hospital discharge	5 (1.9%)	11 (4.0%)	2.2 (0.7–6.3)	0.15
CPC 1 or 2	5 (100%)	9 (81.8%)	n/a	0.31

Table 3
Patient outcomes for adrenaline versus placebo by shockable and non-shockable initial cardiac arrest rhythm.

	Shockable (n = 245)			Non-shockable (n = 289)		
	Placebo	Adrenaline	OR (95% CI) p-Value	Placebo	Adrenaline	OR (95% CI) p-Value
ROSC achieved pre-hospital	17 (13.5%)	32 (26.9%)	2.4 (1.2–4.5) p = 0.009	5 (3.7%)	32 (20.9%)	6.9 (2.6–18.4) p < 0.001
Admitted to hospital	19 (15.1%)	33 (27.7%)	2.2 (1.2–4.1) p = 0.01	15 (11%)	36 (23.5%)	2.5 (1.3–4.8) p = 0.005
Survived to hospital discharge	5 (4.0%)	9 (7.6%)	2.0 (0.6–6.0) p = 0.23	0 (0%)	2 (1.3%)	n/a

riers associated with trialling interventions deemed “standard of care” where clinical equipoise clearly exists serves only to ensure such interventions remain unproven. The findings of this study are clinically important in that it establishes efficacy for the continued use of adrenaline in cardiac arrest as currently recommended, however numerous questions remain unanswered. Cardiac arrest is a disease entity that rapidly moves through a number of phases for which targeted interventions may further optimise survival.²³ We have yet to determine the optimal dose or timing of adrenaline during cardiac arrest. This study provides an evidence base for current practice and a platform for ongoing research.

5. Conclusion

The use of adrenaline in cardiac arrest significantly improves the proportion of patients achieving ROSC prehospital, but failed to demonstrate a better survival to hospital discharge, possibly due to inadequate sample size. Further studies on the role of adrenaline in cardiac arrest are required to determine optimal dose and timing for drug administration.

Conflicts of interest

No conflicts of interest to declare.

Acknowledgements

The investigators would like to acknowledge the support of St John Ambulance Western Australia and the paramedics who were willing to participate in the study. Appreciation is extended to: Pharma Laboratories who prepared the adrenaline and placebo vials; to and Laraine Salo and Tena Rowe who undertook data entry; and to Dr Tiew-Hwa Teng who derived the CPC scores. This study was funded by the National Health and Medical Research Council (Grant No. 254537). The funding body had no involvement in any aspect of study design, conduct or analysis. The results of this study were presented at the American Heart Association Resuscitation Science Symposium in Chicago in 2010 and the European Resuscitation Council Resuscitation Congress 2010 in Porto.

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