Repeated adrenaline doses and survival from an out-of-hospital cardiac arrest

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ABSTRACT

Background – Adrenaline is the primary drug of choice for resuscitation from out-of-hospital cardiac arrest (OHCA). Although adrenaline may increase the chance of achieving return of spontaneous circulation (ROSC), there is limited evidence that repeated doses of adrenaline improves overall survival, and increasing evidence of a detrimental effect on neurological function in survivors. This paper reports the relationship between repeated doses of adrenaline and survival in a cohort of patients attended by the London Ambulance Service in the United Kingdom.

Methods – A retrospective review of OHCA treated by the London Ambulance Service over a one year period. Patients aged ≥18 years who received one or more doses of adrenaline (1 mg bolus) during resuscitation were included in the analyses. Outcomes described are survival to hospital discharge and survival to one year post-arrest.

Results – Over the one year study period, 3,151 patients received adrenaline during OHCA. A significant inverse relationship was found between increasing cumulative doses of adrenaline and survival both to hospital discharge and one year post-arrest. No patients survived after receiving more than ten adrenaline doses.

Conclusion – Our study indicates that repeated doses of adrenaline are associated with decreasing odds of survival. There were no survivors amongst patients requiring more than 10 doses of adrenaline.

INTRODUCTION

The administration of adrenaline has been the cornerstone of treatment for out-of-hospital cardiac arrest (OHCA) for decades[1]. Resuscitation guidelines worldwide recommend the use of adrenaline, administered every 3-5 minutes, as part of advanced life support for cardiac arrest from all causes and all rhythms[2-5].

Evidence for a short-term beneficial effect of adrenaline in achieving return of spontaneous circulation (ROSC) after an OHCA has been reported in several observational studies and meta-analyses[6-11]. Notably, the recent randomised, double-blind PARAMEDIC2 trial, conducted within ambulance services in the United Kingdom (UK), found a higher rate of ROSC, with a small increase in survival to hospital discharge (<1%)[12], something supported by two previous randomised studies[13, 14].

Irrespective of any effect on survival, concern about the use of adrenaline in OHCA has been growing, with accumulating evidence indicating that its use may be harmful, particularly in terms of poorer neurological functioning[7, 9, 15-17].

There are also questions around the quantities and numbers of doses of adrenaline given. One French study reported no difference in survival between repeated administrations of high-dose (5mg) adrenaline and standard-dose (1mg) adrenaline[18], while reporting a slight increase in ROSC in the high-dose group. Another study from America reported higher rates of survival with less frequent administration of adrenaline than the recommended 3-5 minutes frequency of administration, indirectly suggesting that larger amounts of adrenaline may have poorer outcome.

Our study sought to examine the relationship between repeated (1mg) doses of adrenaline and survival, and explore whether there is a point during OHCA after which the administration of further doses, as currently recommended, becomes futile.

METHODS

Study design

A retrospective, observational analysis using anonymised data from the London Ambulance Service (LAS) cardiac arrest registry over a one-year period (1st April 2012–31st March 2013). Ethical approval was not required as this study used data routinely collected for clinical audit purposes.

Patient population

All adult patients (≥18 years of age) who experienced an OHCA of presumed cardiac aetiology, and received one or more doses of adrenaline (1 mg bolus) during resuscitation, were eligible for inclusion in this study.

Study setting

The LAS covers the geographical area of Greater London, UK, which spans approximately 620 square miles and serves a population of 8.4 million people[19]. During the study period, more than 1 million incidents were attended by the LAS[20], with over 10,000 of these being OHCA[21].

Calls identified as 'cardiac arrest' (using the advanced Medical Priority Dispatch System) receive the highest level response, with a minimum of two emergency vehicles, staffed by at least one paramedic (trained in advanced life support), being dispatched to the incident.

All LAS clinicians operate to the Resuscitation Council (UK) guidelines[2], which advise the administration of adrenaline (intravenous or intraosseous) for all initial rhythms during an OHCA. If the patient presents in ventricular fibrillation or pulseless ventricular tachycardia (VF/pVT), a 1 mg bolus of adrenaline is administered after 3 unsuccessful defibrillation attempts, whereas for non-shockable rhythms (pulseless electrical activity (PEA) or asystole) a 1 mg bolus of adrenaline is administered as soon as possible. If the cardiac arrest persists, a further dose of adrenaline is advised every 3-5 minutes with no upper dose limit until either ROSC is achieved and the patient is handed over to hospital, or the resuscitation attempt is terminated. If ROSC is achieved, local LAS protocol allows a lower dose of adrenaline (0.1 mg bolus) to be administered to maintain the patient's blood pressure and prevent re-arrest.

Data collection

Data were obtained from the LAS Out-of-Hospital Cardiac Arrest Registry that collates patient, process, treatment and outcome information from multiple sources (including emergency dispatch call logs, and ambulance service and hospital clinical patient records) to provide a comprehensive clinical record for each OHCA. Characteristics and outcomes recorded include: patient demographics,

location of arrest, presenting cardiac rhythm, bystander intervention, pre-hospital resuscitation methods, ROSC and survival to hospital discharge. Long-term outcome, with survival up to 1 year post-arrest, was obtained from NHS Digital Summary Care Records.

Data analysis

Data analysis and statistics were performed using Excel (Microsoft, Redmond, WA), SPSS v23 (IBM, Armonk, NY) and R 3.5.1 (A Language and Environment for Statistical Computing). Statistical significance was accepted when $p<0.05$.

The association between percentage survival (to hospital discharge and to one year post-arrest) and independent explanatory variables was assessed using a step-wise multivariate logistic regression model. We first undertook univariate logistic regressions on all known predictors of survival (age, sex, adrenaline dose group, initial shockable rhythm, time from EMS call to first adrenaline dose, ROSC, bystander CPR, and witness status). We then built a step-wise multivariate regression model starting with the predictor that had the strongest association with the outcome based on the partial F-tests obtained from the regression. At each step we added the predictor that had the next strongest association or excluded the predictor that no longer explained the outcome. We stopped this procedure when no more predictors could be added or removed, and this is the final model upon which the results are based. Collinearity between the predictors was assessed by calculating the variance inflation factor (VIF) for each predictor and excluding those variables that had a VIF greater than 5. No predictor met this criterion and therefore none were removed from analysis based on collinearity. The number of doses of adrenaline were categorised into three categories, 1 dose, 2 doses, and >3 doses in the multivariate analysis.

When presenting results, continuous variables are presented as means ± standard deviation (SD) and categorical variables are reported as counts with relative frequencies. Adjusted odds ratios (AOR) and 95% confidence intervals (CI) obtained from the multi-variable binomial logistic regression after controlling for potential confounders were used to interpret associations between variables and outcomes.

RESULTS

Resuscitation was attempted for 4,466 OHCA patients; with 3,151 (71%) meeting the criteria for inclusion in the study (see Figure 1). In total, 137 (4.3%) patients survived to be discharged from hospital, with 108 of 122 patients (88.5%; with 15 lost to follow up) still alive at one year (representing 3.4% overall). Patient demographics and key event characteristics based on patient outcome are summarised in Table 1. Compared to non-survivors, those who survived to one year had almost four fewer doses of adrenaline on average ($p<0.001$), presented with an initial shockable rhythm (VF/VT) ($p<0.0001$), were more likely to have had a witnessed arrest ($p<0.001$), received a higher number of shocks ($p<0.001$) and had an 'EMS call' to 'administration of first adrenaline dose' interval that averaged five minutes faster ($p<0.001$).

Each one minute of delay from 'EMS' call to 'administration of first adrenaline dose' was associated with a 7% reduction in survival (OR = 0.93; CI = 0.91, 0.96; $p<0.0001$) to both hospital discharge and one year post arrest. However, this association was no longer significant after adjusting for other covariates in the multivariate regression model (AOR = 0.98; CI = 0.95, 1.00; $p=0.09$).

Association of repeated doses of adrenaline and survival

The relationship between repeated adrenaline doses and survival both to hospital discharge and to one year post-arrest is presented in Figure 2 and Supplementary Table 1. The number of adrenaline doses administered had a negative association with both measures of survival. Survival to hospital discharge was approximately 20% with one dose of adrenaline, rapidly declining to less than 2% at five or more doses. Survival to one year followed a similar pattern. There were no survivors amongst patients who received more than 10 doses of adrenaline.

While there were variables listed in Table 1 that were significantly associated with survival at the univariate level, only adrenaline dose group, presence of an initial shockable rhythm, age and sex could significantly predict survival in the step-wise regression model. Therefore we present association of adrenaline dose group with survival after adjusting for the significant confounders, initial shockable rhythm, age and sex.

Multivariate analysis revealed that when adjusted for the effects of age, sex, and an initial shockable rhythm, three or more doses of adrenaline were associated with an 85% decrease in the likelihood of surviving to hospital discharge (AOR = 0.15; CI = 0.09, 0.26; $p<0.0001$) and an 82% decrease in surviving to one year (AOR = 0.18; CI =0.1, 0.11; $p<0.0001$). Full analysis results are detailed in Table 2.

Two patients (out of 190; 1.1%) who received 9 doses of adrenaline, and a further 2 patients (out of 224; 0.9%) who received exactly 10 doses of adrenaline, survived to hospital discharge and were still

alive at one year (see Supplementary Table 2 for details of these patients). The first dose of adrenaline was administered to all four patients in less than 13 minutes from initiation of CPR, well within the overall average (15 minutes). All cases had an end-tidal carbon dioxide ($ETCO_2$) value over 20 mmHg with Cases 1 and 3 exceeding 30 mmHg. Case 2, 3 and 4 had intermittent ROSC during resuscitation, with Cases 1, 2 and 3 achieving a stable ROSC which was sustained from the arrest location to hospital handover. In addition, the three patients who suffered a myocardial infarction (Cases 1, 2 and 4) were conveyed by ambulance directly to a specialist heart attack centre for coronary intervention.

A total of 267 patients received more than 10 doses of adrenaline, and none survived. Using the 'rule of three'[22] our study predicts that more than 10 doses of adrenaline will result in no more than 1.1% (95% CI 0-1.1) of patients surviving to hospital discharge and one year post arrest.

DISCUSSION

This study sought to describe the association between repeated doses of adrenaline and survival. We found that three or more doses were associated with a significant reduction in the odds of surviving to both hospital discharge and to one year post-arrest. The decline in survival was evident up to five cumulative doses of adrenaline, at which point the relationship flattened due to very few survivors, with no survivors after ten doses. The significant inverse relationship between cumulative doses of adrenaline and survival persisted even after adjusting for potential confounders using multivariate analysis.

These results support the findings of Glover et al[23] who described an independent negative association between the probability of survival to hospital discharge and adrenaline dose in the US and Canada. We found four patients who, despite a higher number of adrenaline doses (9 or 10 doses), were still alive one year post-arrest. However, it is likely that the favourable factors observed (which included a reversible cause of arrest, conveyance to a specialist centre, and a short time to first adrenaline dose) contributed to their survival.

While in our study, 'EMS call' to 'administration of first adrenaline dose' interval was not significantly associated with survival after adjusting for confounders, previous studies have identified a relationship between time to first dose of adrenaline and survival [24-28] in their multivariate models. Hubble et al observed a 4% reduction in the odds of obtaining ROSC for every one minute delay from emergency call to administration of a vasopressor[24]. Two other studies suggested that, when administered within 20 minutes of the emergency call, repeated doses of adrenaline were associated with improved neurological outcome for witnessed cardiogenic OHCA[25, 26]. Hayashi et al further demonstrated that for patients in VF/VT[27], administration of adrenaline within 10 minutes of the emergency call was associated with better one-month neurological outcome[28]. In our study, those who survived to one year had an 'EMS call' to 'first adrenaline dose' time interval that was, on average, five minutes faster compared to those who died. It is to be noted however, that variables used to build multivariate models differed in all these studies and perhaps could explain the difference in results.

Being an observational study, we were unable to separate the effect of the number of adrenaline doses, from the length of time a patient was in cardiac arrest and the severity of their condition, both of which are known to influence outcome[29]. As such, our findings must be interpreted with caution. It is likely that cumulative doses of adrenaline are a proxy for cardiac arrest duration, which is associated with increasingly poor outcome, a phenomenon that has been termed 'resuscitation time bias'[29]. However, given that adrenaline increases the likelihood of achieving ROSC, these two variables are heavily interdependent. The observed effects may also be attributed to other unknown confounders.

There are further limitations in the data available for our study. We were unable to obtain neurological outcomes from hospitals, and this would have provided a valuable insight into the neurological effects of cumulative adrenaline doses and the quality of life for OHCA survivors. Technological limitations within our EMS system prevented defibrillator downloads from being available for analysis; these data would have enabled us to assess the quality of CPR, something which may have impacted on drug delivery and subsequent efficacy[30].

Despite the limitations, our findings support the need for further research into the efficacy, timing and dosage of adrenaline during resuscitation. Current guidelines recommend administration of adrenaline (1 mg) every 3-5 minutes[2]; however, in-hospital studies suggest that a less frequent dosing strategy may increase survival[31] and could reduce development of secondary VF/VT[32]. One study comparing high-dose adrenaline (15mg) with the standard dose (1 mg), documented an increase in ROSC and survival to hospital admission with the higher dose[33]. In contrast, Frisk et al investigated a lower adrenaline dose (0.5 mg), which did not affect survival to hospital discharge or favourable neurological outcome for OHCA patients[34]. It is clear that the optimum dose of adrenaline is a knowledge gap that needs further investigation[35].

Conclusion

Our study indicates that repeated doses of adrenaline are associated with decreasing odds of survival. There were no survivors amongst patients requiring more than 10 doses of adrenaline.

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FIGURE LEGENDS

Figure 1. Overview of cases meeting our inclusion criteria and outcomes.

Figure 2. Relationship between the number of adrenaline doses and percentage survival to hospital discharge and survival to 1-year post-arrest. Shaded regions represent 95% confidence interval. 33 unknown outcomes were excluded from analysis.

TABLE LEGENDS

Table 1. Patient demographics and key event characteristics for out-of-hospital cardiac arrests (OHCA) where one or more dose of adrenaline (1 mg) was administered during resuscitation. Univariate analysis was used to compare patients who survived to 1 year and those who died. 33 cases were excluded from analysis due to unknown outcomes. SD, standard deviation; CPR, cardiopulmonary resuscitation; EMS, emergency medical service; VF, ventricular fibrillation; pVT, pulseless ventricular tachycardia; PEA, pulseless electrical activity.

Table 2. Adjusted odds ratios (AOR) for survival to hospital discharge and 1 year post-arrest. Multivariate analysis was used to control for potential confounders listed on Table 1. †An adjusted odds ratio above 1.0 favors survival. SD, standard deviation; CI, confidence interval.

SUPPLEMENTARY FIGURES

Supplementary Table 1. Cardiac arrest cases attended from 2012-2013 by the London Ambulance Service: doses of adrenaline and return of spontaneous circulation (ROSC) sustained to hospital, outcome hospital discharge and 1 year post-arrest for all initial rhythms. All percentages were calculated as a percentage of total counts for each adrenaline dose.

Supplementary Table 2. Case review of patients who received 9 or 10 doses of adrenaline for an out-of-hospital cardiac arrest and survived. M, male; CPR, cardiopulmonary resuscitation; VF, ventricular fibrillation; VT, ventricular tachycardia; PEA, pulseless electrical activity; EMS, emergency medical service; ROSC, return of spontaneous circulation.

Supplementary Table 3. Cardiac arrest cases attended from 2012-2013 by the London Ambulance Service: doses of adrenaline and outcome at 1 year post-arrest are broken down by initial rhythms. All percentages were calculated as a percentage of total counts for each adrenaline dose.

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