



High dose versus standard dose epinephrine in cardiac arrest — a meta-analysis

C. Vandycke*, P. Martens

Department of Emergency Medicine, AZ-St Jan, Brugge, Belgium

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Abstract

In the management of cardiac arrest there is ongoing controversy concerning the optimal dose of epinephrine. To obtain the best available evidence regarding the current optimal dose, we performed a meta-analysis. We searched the Medline database online and reviewed citations in relevant articles to identify studies that met preset inclusion criteria (prospective, randomized, double-blind). Five trials were identified. The pooled odds ratio for return of spontaneous circulation favours the experimental dose. The pooled odds ratio for hospital discharge failed to demonstrate a statistically significant beneficial effect of high and/or escalating doses of epinephrine in comparison with standard dose of epinephrine. The possibility that patients who have already sustained irreversible neurologic injury will be resuscitated carries potential adverse social and economic implications. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Although epinephrine has been used as a standard first-line drug in cardiac arrest for several decades, the optimal dose of epinephrine for the three main categories of adult cardiac arrest (persistent ventricular fibrillation, pulseless electrical activity and asystole), has not yet been definitely determined. Animal studies and human case reports suggest that high dose epinephrine might be more effective than the doses recommended by the European Resuscitation Council, and the American Heart Association in maintaining coronary and cerebral perfusion pressure and in restoring spontaneous circulation [1–3]. These preliminary reports precipitated the introduction of epinephrine in large dose vials.

Moreover, the fact that high dose epinephrine might merely result in longer hospital stay, but no

improvement in neurologic outcome or discharge rate from the hospital, is an additional area of growing concern [4–9]. In an attempt to reach the best level of evidence regarding this issue, we conducted a meta-analysis concerning the usage of high dose epinephrine versus standard dose epinephrine in the management of cardiac arrest in humans.

2. Methods

2.1. Data abstraction

We searched the Medline database online, from January 1988 to December 1998, to identify all English-language articles with the medical subject headings; ‘epinephrine’ ‘high dose’–‘randomized, double blind, controlled trial’–‘human’.

Randomized controlled trials are recognized as the most valid assessment of the efficacy of a new treatment. All the potentially relevant original articles were reviewed. The authors of the primary

* Corresponding author. Present address: Department of Anaesthesia and Critical Care, AZ St Jan Hospital, Ruddershove 10, 8000 Brugge, Belgium.

studies were not contacted to identify additional studies. Only five studies dealing with out-of-hospital cardiac arrest patients meeting the criteria of adult, prospective, randomized, double-blind clinical trials published in journals with a high impact factor, were withdrawn for further analysis (Table 1) [10–14]. Other studies were small, retrospective and/or inhomogeneous with regard to the study population, were only published as abstracts, or did not meet methodological standards for clinical trials. [15–21]

2.2. Outcome measures

Data were obtained according to the Utstein guidelines for reporting out-of-hospital cardiac arrest events [22]^[JDVI] The following primary outcome measures were considered as successful: return of spontaneous circulation (ROSC), defined as the return of a palpable pulse and blood pres-

sure for at least 4 min, admission to hospital, discharge from hospital alive, with cerebral performance category (CPC) I (fully functional) or II (conscious with only moderate cerebral disability). Death, CPC III (severely disabled) and IV (vegetative state) were considered as unsuccessful. Outcome was used as a measure of the relation between the dosage (standard versus high or escalating) of epinephrine and improved survival.

2.3. Statistical analysis

Odds ratios (OR) with their 95% confidence interval (CI) were used as a measure of the relative beneficial effect on outcome of experimental dose epinephrine versus standard dose. The odds ratio can equal any non-negative number. The value 1 corresponding to independence serves as a baseline for comparison. In case-control studies, the relative risk cannot be evaluated directly but, in many

Table 1
Characteristics of the five studies we withheld for our meta-analysis

Authors	Journal	Years and principal location of study	Study design	number of subjects	Dose	Hospital discharge (%)
Gueugniaud et al.	N. Engl. J. Med.	1994–1996, France and Belgium	Randomized, prospective, multi-centred, out of hospital, double blind	Experimental dose, 1677	5 mg	8.6
				Standard dose, 1650	1 mg	11.8
Choux et al.	Resuscitation	1991–1992, Lyon (France)	Randomized, prospective, out-of hospital, double blind	Experimental dose, 271	5 mg	9.2
				Standard dose, 265	1 mg	5.5
Brown et al.	N. Engl. J. Med.	1989–1990, Houston, OH, Wisconsin, Washington, Virginia, NY	Randomized, prospective, multi-centred, out-of hospital, double blind	Experimental dose, 648	0.2 mg/kg	21.4
				Standard dose, 632	0.02 mg/kg	19.1
Stiell et al.	N. Engl. J. Med.	1989–1992, Canada	Randomized, prospective, multi-centred, out-of hospital, double blind	Experimental dose, 317	7 mg	17.9
				Standard dose, 333	1 mg	21
Callaham et al.	J. Am. Med. Assoc.	1990–1992, San Francisco	Randomized, prospective, multi-centred, out-of hospital, double blind	Experimental dose, 286	15 mg	16.6
				Standard dose, 260	1 mg	14.3

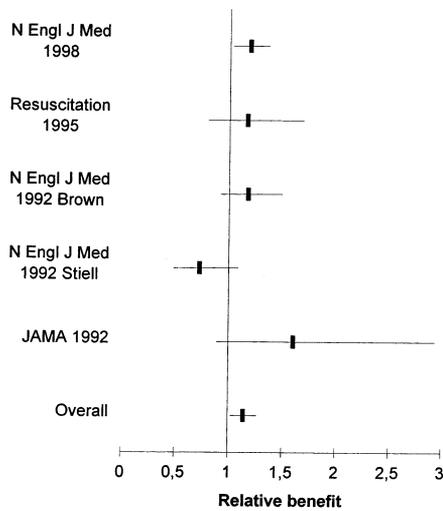


Fig. 1. OR and 95% CI for ROSC.

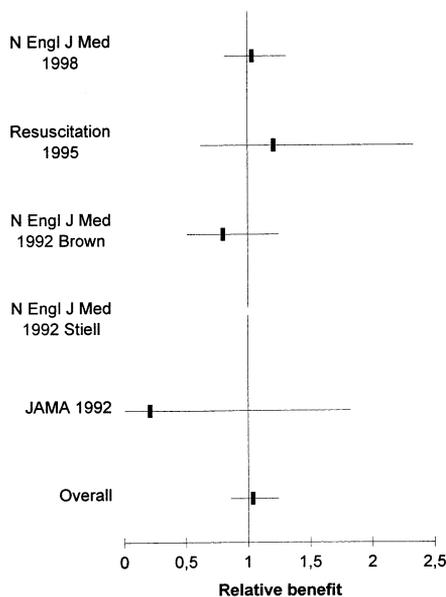


Fig. 2. OR and 95% CI for hospital admissions.

circumstances, the odds ratio is a good approximation to the relative risk. The odds ratio can be thought of as odds in favour of having a benefit from the experimental therapy and it is often referred to as approximate relative risk. Odds ratios on each side of 1 reflect certain types of associations. Values further from 1 in a given direction represent stronger levels of association.

An exact two-tailed P value < 0.05 was considered to indicate statistical significance. When 1 is not included in the CI, the OR was considered as significant. The statistical software package used was STATXACT-3, and plots (figures) were made on a personal computer.

3. Results

Of the five studies, recruiting patients between 1989 and 1996 included, four were multi-centred, two were European and three were North American. The number of subjects per study ranged from 536 to 3327. The bolus dose of experimental epinephrine ranged from 5 to 15 mg. Hospital discharge ranged from 8.6 to 21.4% in the experimental group, and from 5.5 to 21% in the standard group.

Figs. 1–3 show the odds ratios and the 95% confidence intervals of, respectively, achieving ROSC, hospital admission and discharge alive (CPC I, II). Considering ROSC as an outcome measure, we calculated an OR exceeding 1 in four studies. Although only one (French) study produced an OR reaching statistical significance, the pooled OR became even more statistically significant (Table 2). Considering admission to hospital and hospital discharge, not one statistically significant OR could be observed (Tables 3 and 4). Moreover, the pooled OR for hospital discharge showed a trend favouring the standard dose of epinephrine.

4. Discussion

So far, the randomized studies of high or escalating dose epinephrine have shown no significant improvement in hospital discharge. If there is a trend, it favours standard doses [23–25].

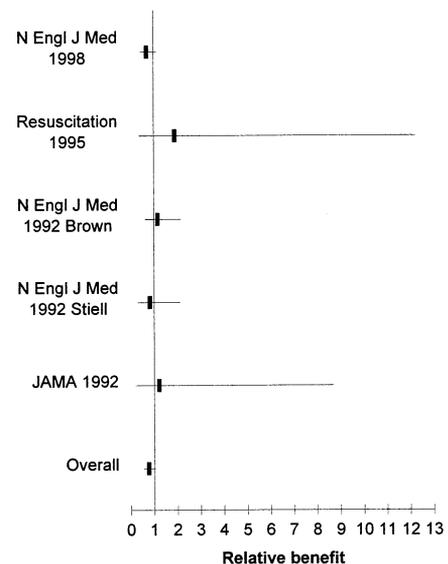


Fig. 3. OR and 95% CI for hospital discharge.

Table 2
OR and 95% confidence interval for ROSC in the different studies, and the pooled OR and 95% confidence interval

Studies included	Odds ratio and 95% confidence interval	<i>P</i> value
N. Engl. J. Med., 1998	1.19 (1.03–1.37)	0.01933
Resuscitation, 1995	1.16 (0.79–1.69)	0.4665
N. Engl. J. Med., 1992 (Stiell)	1.17 (0.92–1.49)	0.2093
N. Engl. J. Med., 1992 (Brown)	0.72 (0.48–1.09)	0.1241
J. Am. Med. Assoc., 1992	1.60 (0.89–2.94)	0.1248
Overall	1.14 (1.02–1.27)	0.01632

Table 3
OR and 95% confidence interval for admission to the hospital in the different studies, and the pooled OR and 95% confidence interval

Studies include	Odds ratio and 95% confidence interval	<i>P</i> value
N. Engl. J. Med., 1998	1.03 (0.82–1.31)	0.8207
Resuscitation, 1995	1.20 (0.62–2.33)	0.6636
N. Engl. J. Med., 1992 (Stiell)	0.80 (0.51–1.25)	0.3532
N. Engl. J. Med., 1992 (Brown)	No data available	
J. Am. Med. Assoc., 1992	0.20 (0.004–1.82)	0.2391
Overall	1.03 (0.86–1.24)	0.7485

Table 4
OR and 95% confidence interval for hospital discharge in the different studies, and the pooled OR and 95% confidence interval

Studies included	Odds ratio and 95% confidence interval	<i>P</i> value
N. Engl. J. Med., 1998	0.70 (0.43–1.12)	0.1482
Resuscitation, 1995	1.89 (0.38–12.22)	0.6009
N. Engl. J. Med., 1992 (Stiell)	1.15 (0.62–2.16)	0.7478
N. Engl. J. Med., 1992 (Brown)	0.82 (0.30–2.12)	0.8198
J. Am. Med. Assoc., 1992	1.20 (0.20–8.70)	1.000
Overall	0.74 (0.53–1.03)	0.08006

Why human trials are not in accordance with animal studies remains unclear [26]. The slight differences in the experimental treatment (different dose regimes, e.g. a total of 5, 7 and 15 mg, and 0.2 mg/kg) together with the variability in the investigated population are generally considered as the major limitations of using the meta-analysis technique. For example, outcome in the French trial was already markedly poorer than in the other trials, leaving the authors with a population for which the potential for improvement was greater than others. Even the intervals between doses are not standardized. Nevertheless, the controversy around the epinephrine dose, in our opinion, does not suffer from publication bias (i.e. the greater likelihood of publication of positive results than negative results).

Apart from the well-known drawbacks of using this technique to solve therapeutic questions in acute medicine, we would like to focus on the following particular difficulties with epinephrine trials: first, cardiac arrest is a denominator of a variety of clinical entities: clearly coarse ventricular fibrillation of recent onset or sudden complete atrioventricular block are very different clinical situations from long-standing fine ventricular fibrillation or asystole.

Other factors such as prompt recognition of the arrest, bystander cardiopulmonary resuscitation, rapid arrival of first responders with defibrillation capabilities, female sex and arrival of skilled Advanced Cardiac Life Support units have been proven to increase survival [27–29].

Therefore, pharmacologic treatment should ideally be titrated or adjusted to the characteristics of the cardiac arrest victims, such as first present rhythm, frequency and amplitude of the ventricular fibrillation, underlying disease, cause of cardiac arrest. Blinding with respect to treatment assignment throughout the trial precludes the use of a titratable continuous infusion.

Although we did not give an overall quality score to each trial, the duration and the quality of ROSC is ill-defined in several trials (in the French study of Choux; Resuscitation 1995, the duration of ROSC is not stated). Most large clinical studies so far failed to focus on a population whose outcome could be improved by an innovative treatment. This is not only the case for the dose of epinephrine, but also for anti-arrhythmic drugs (e.g. bretylium, amiodarone) and the active compression–decompression device [30].

The inclusion of patients whose outcome is uniformly bad, irrespective of any treatment, will, even in very large randomized trials, negate a potential beneficial effect in suitable candidates.

Given the absence of large trials with a significant improvement in favour of high doses (i.e. hospital discharge rate increased by 25%), a worldwide trial is ideally needed to assess whether epinephrine dosage has a modest impact on overall survival or improves results only for a subset of cardiac arrest patients [31].

Perhaps the time has come to compare alternative drugs with epinephrine, such as vasopressin, in the treatment of sudden human cardiac death.

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