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Efficacy of vasopressin-epinephrine compared to epinephrine alone for out of hospital cardiac arrest patients: A systematic review and meta-analysis

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ABSTRACT

Objective: The aim of this study was to conduct a meta-analysis to evaluate the efficacy of vasopressin-epinephrine compared to epinephrine alone in patients who suffered out-of-hospital cardiac arrest (OHCA).
Methods: Relevant studies up to February 2017 were identified by searching in PubMed, EMBASE, the Cochrane Library, Wanfang for randomized controlled trials(RCTs) assigning adults with cardiac arrest to treatment with vasopressin-epinephrine (VEgroup) vs adrenaline (epinephrine) alone (E group). The outcome point was return of spontaneous circulation (ROSC) for patients suffering from OHCA. Heterogeneity, subgroup analysis, sensitivity analysis and publication bias were explored.
Results: Individual patient data were obtained from 5047 participants who experienced OHCA in nine studies. Odds ratios (ORs) were calculated using a random-effects model and results suggested that vasopressin-epinephrine was associated with higher rate of ROSC (OR = 1.67, 95% CI = 1.13–2.49, P < 0.00001, and total I^2 = 83%). Subgroup showed that vasopressin-epinephrine has a significant association with improvements in ROSC for patients from Asia (OR = 3.30, 95% CI = 1.30–7.88); but for patients from other regions, there was no difference between vasopressin-epinephrine and epinephrine alone (OR = 1.07, 95% CI = 0.72–1.61).
Conclusion: According to the pooled results of the subgroup, combination of vasopressin and adrenaline can improve ROSC of OHCA from Asia, but patients from other regions who suffered from OHCA cannot benefit from combination of vasopressin and epinephrine.

Contents

1. Introduction . . . 0
2. Methods . . . 0
2.1. Search strategy . . . 0
2.2. Selection criteria . . . 0
2.3. Risk of bias in individual studies . . . 0
2.4. Data extraction . . . 0
2.5. Statistical analysis . . . 0
3. Results . . . 0
3.1. Study selection . . . 0
3.2. Study characteristics . . . 0
3.3. Assessed intervention . . . 0
3.4. Risk of bias in included studies . . . 0
4. Discussion . . . 0
5. Conclusion . . . 0
Author contributions . . . 0

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1. Introduction

Out-of-hospital cardiac arrest (OHCA) is an important health concern in aging societies [1]. It is associated with very high mortality and a high incidence of neurological injury to the survivors. In recent years, choice of drugs after cardiac arrest has been controversial for out-of-hospital cardiac arrest. Historically, epinephrine has been the vasopressor agent of choice for cardiopulmonary resuscitation, but the prognosis of patients with cardiac arrest who require epinephrine remains extremely poor, regardless of the cumulative epinephrine dose given [2].

Because endogenous vasopressin levels were found to be significantly higher in successfully resuscitated patients than in patients who died, Lindner et al. suggested that it might be beneficial to administer vasopressin during cardiopulmonary resuscitation [3]. However clinical trials have produced conflicting results about the effects of vasopressin on outcomes in patients with OHCA.

Recent interest has shifted to the possibility of a benefit of using both vasopressin and adrenaline over adrenaline alone. Specifically, the combination increases coronary the perfusion pressure, improves the return of spontaneous circulation [4], increases the survival [5,6], improves cerebral blood flow [7], increases diastolic aortic pressure and improves neurological outcomes compared to epinephrine or vasopressin alone. These findings stimulated the researchers' interest in finding a correlation between use of this combination and the return of spontaneous circulation in human cardiac arrest. In one of these clinical studies [8], successive administration of vasopressin and epinephrine in a subgroup of patients with refractory cardiac arrest resulted in significantly higher rates of survival to hospital discharge than repeated injections of epinephrine alone, suggesting that combined administration of vasopressin and epinephrine during cardiopulmonary resuscitation might be an effective strategy to improve the outcome. Francis et al. demonstrated that there is an association between using vasopressin in combination with epinephrine and restoration of circulation after out-of-hospital cardiac arrest [9]. However, a more recent OHCA trial explored and found that the combination of vasopressin and adrenaline did not improve the outcome for OHCA compared to adrenaline alone [10].

Although many studies have explored the association between vasopressin-epinephrine and outcomes in OHCA patients, there is a significant degree of contradiction in the existing literature. A meta-analysis from 2008 by Victoria et al. was conducted to compare the efficacy of vasopressin and epinephrine used together versus repeated doses of epinephrine alone in IHCA and OHCA patients [11], and it only included three articles. The conclusions are not scientifically sound and are very misleading. Therefore, it is worthwhile to perform an update systematic review. The aim of this study was to compare the efficacy of the combination of vasopressin-epinephrine to epinephrine alone in patients who experience out of hospital cardiac arrest.

2. Methods

2.1. Search strategy

The PubMed, EMBASE, the Cochrane Library, Wanfang were searched up to February2017. Terms used for the search were “pitressin” “vasopressin” “Epitrate” “epinephrine” or “adrenaline” in conjunction with “asystole” “cardiac arrest” “heart arrest” “cardiopulmonary arrest” and “Related articles”. The list of references was also used to identify additional studies.

2.2. Selection criteria

All studies were selected by two independent reviewers according to the following criteria: (a) studies of randomized clinical trials involving cardiac arrest, comparing the efficacy of vasopressin-epinephrine and epinephrine alone (b) the clinical outcomes of interest included ROSC, (c) the full paper could be obtained; (d) there were sufficient published data for estimating the odds ratio (OR) with the 95% CI; (e) for duplicate publications, the largest or most recent publication was selected; (f) the subjects were patients with OHCA; (g) studies published in English or Chinese. Studies were excluded if they did not meet the above requirement.

2.3. Risk of bias in individual studies

The methodological quality of the RCTs was assessed independently using the Cochrane Handbook for Systematic Reviews of Interventions [updated September 2009]. Two investigators independently evaluated the methodological quality of the included articles. Disagreements were resolved through consensus or discussed with a third author. Risk of bias in individual studies is shown in Table 1.

2.4. Data extraction

Data were extracted by two independent reviewers from each eligible study. The requested information included the first author's name, publication year, country, study design and outcomes.

2.5. Statistical analysis

The efficacy was estimated for each study by the odds ratio (OR) along with its 95% CI. The pooled OR and 95% CI were calculated by the fixed-effect model using the Mantel Haenszel method [12] when heterogeneity was not present (PQ ≥ 0.1 or $I^2 \leq 50\%$), otherwise we used a random-effect model with the Dersimonian and Laird method [13] (PQ < 0.1 or $I^2 > 50\%$). Subgroup analysis and sensitivity analysis were used to explore the sources of heterogeneity. The influence of individual studies on the pooled OR was estimated by reestimating and plotting in the absence of each study. Publication bias was assessed using funnel plots and Egger's test. All the analyses were performed using Review Manager software (version 5.3), with a two-sided $P < 0.05$ considered statically significant. Heterogeneity was assessed using the Q-test [14] based on the Chi-square or I^2 statistic test.

Table 1
The methodological quality of included studies based on the Cochrane handbook.

Author/year	A	B	C	D	E	F	G	H
Ongme 2012	?:	−	+	+	+	−	−	?:
Gueugniaud 2008	?:	−	+	+	?:	+	−	−
Callaway 2006	?:	−	−	−	−	+	−	−
Wenzel 2004	?:	−	+	+	+	+	−	−
Ducros 2011	?:	−	?:	?:	−	+	−	−
Yang 2012	?	?	+	?	?	?	?	?
He 2010	?	?	+	?	?	?	?	?
Hu 2008	?	?	+	?	?	?	?	?
Xiao 2007	?	?	+	?	?	?	?	?

A: adequate sequence generation; B: concealment of allocation; C: blinding (patient); D: blinding (investigator); E: blinding (assessor); F: incomplete outcome data addressed (ITT analysis); G: free of selective reporting; H: other potential there at to validity. +: yes, −: no, ?: unclear.

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