

BMJ Open Therapeutic effects of vasopressin on cardiac arrest: a systematic review and meta-analysis

Wenqing Yan ,^{1,2} Weihua Dong,¹ Xin Song,^{1,2} Wenqiang Zhou,^{1,2} Zhi Chen ¹

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¹Department of Emergency, Jiangxi Provincial People's Hospital, Nanchang, Jiangxi, People's Republic of China

²Medical Department, Nanchang University, Nanchang, Jiangxi, People's Republic of China

Correspondence to

Dr Zhi Chen;
zhichen@tongji.edu.cn and
Dr Weihua Dong;
Dong@email.ncu.edu.cn

ABSTRACT

Objective To demonstrate the therapeutic effect of vasopressin as an alternative treatment for cardiac arrest.

Design Systematic review and meta-analysis.

Methods PubMed, EMBASE, the Cochrane Library and Web of Science were searched for randomised controlled trials. The intervention included administration of vasopressin alone or vasopressin combined with epinephrine or vasopressin, steroids and epinephrine (VSE) versus epinephrine combined with placebo as control group. The primary outcome was the return of spontaneous circulation (ROSC). The secondary outcomes included mid-term survival and mid-term good neurological outcome. We conducted subgroup analyses of the primary outcome based on different settings, different study drug strategies and different types of initial rhythm.

Results Twelve studies (n=6718) were included, of which eight trials (n=5638) reported the data on patients with out-of-hospital cardiac arrest and four trials (n=1080) on patients with in-hospital cardiac arrest (IHCA). There were no significant differences between intravenous vasopressin and placebo in the outcomes of ROSC (relative risk (RR): 1.11; 95% CI: 0.99 to 1.26), mid-term survival (RR: 1.23; 95% CI: 0.90 to 1.66) and mid-term good neurological outcome (RR: 1.20; 95% CI: 0.77 to 1.87). However, in the subgroup analysis, intravenous vasopressin as part of VSE can significantly improve the rate of ROSC (RR: 1.32; 95% CI: 1.18 to 1.47) but not the rate of mid-term survival (RR: 2.15; 95% CI: 0.75 to 6.16) and mid-term good neurological outcome (RR: 1.80; 95% CI: 0.81 to 4.01) for patients with IHCA.

Conclusions Our study failed to demonstrate increased benefit from vasopressin with or without epinephrine compared with the standard of care. However, vasopressin as a part of VSE is associated with the improvement of ROSC in patients with IHCA, and the benefit on mid-term survival or mid-term good neurological outcome is uncertain. Larger trials should be conducted in the future to address the effect of vasopressin only, vasopressin plus epinephrine or VSE on cardiac arrest.

PROSPERO registration number CRD42021293347.

BACKGROUND

Cardiac arrest is a major contributor to morbidity and mortality worldwide.¹ For more than 100 years, epinephrine has been administered during cardiopulmonary resuscitation (CPR) for patients in cardiac arrest.²

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study conducted comprehensive evaluation of the effect of vasopressin on cardiac arrest based on different settings, different intravenous vasopressin strategies and different patient types.
- ⇒ The detailed characteristics of the studies including vasopressin dose were summarised.
- ⇒ Mean arterial pressure and long-term outcomes could not be evaluated.
- ⇒ Due to the limited quality of studies and the heterogeneity of study populations, the findings of the study should be cautiously interpreted.

However, previous reports suggested that endogenous vasopressin levels in successfully resuscitated patients were significantly higher than those in patients who died, and that intravenous vasopressin during CPR may give better results than epinephrine.³⁻⁶ Based on a randomised controlled trial (RCT)⁶ and some small case series,^{7,8} the American Heart Association Advanced Cardiac Life Support (ACLS) guidelines⁹ recommend vasopressin as an alternative to epinephrine for the treatment of cardiac arrest. However, the clinical benefit of vasopressin remains debated. A trial by Stiell *et al*¹⁰ showed no obvious benefit of vasopressin over epinephrine for in-hospital cardiac arrest (IHCA). However, a clinical trial¹¹ demonstrated that a combination of vasopressin and epinephrine during CPR improves the outcome for patients with out-of-hospital cardiac arrest (OHCA). In addition, several studies¹²⁻¹⁴ have recently proposed that an emerging therapy using vasopressin, corticosteroid and epinephrine (VSE) during CPR may improve the outcomes for cardiac arrest. To evaluate the impact of vasopressors in patients who had cardiac arrest, a meta-analysis indicated that there was no benefit from vasopressin with or without epinephrine.¹⁵ However, these trials¹²⁻¹⁴ assessing the effect of VSE were not included in the meta-analysis. Currently, there is no systematic review or meta-analysis that has evaluated the

overall therapeutic effect of vasopressin (vasopressin only, vasopressin plus epinephrine and VSE) and the effect based on the type of initial rhythm, witnessed and CPR by a bystander on cardiac arrest. Therefore, we performed a systematic review and meta-analysis to evaluate the therapeutic effect of vasopressin on cardiac arrest.

METHODS

The methods and protocol of this meta-analysis were previously published in detail on the International Prospective Register of Systematic Reviews (registration number: CRD42021293347). Reporting of findings was guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses.¹⁶

Eligibility criteria

Eligibility criteria were based on the Population, Intervention, Control, Outcomes and Study design framework as follows: (1) population—adult patients with cardiac arrest in any setting (IHCA or OHCA); (2) the intervention included administration of vasopressin alone or vasopressin combined with epinephrine or VSE versus epinephrine combined with placebo as control group; (3) the study reported at least one of the following outcomes: return of spontaneous circulation (ROSC), survival and good neurological outcome; and (4) study design: RCTs. The following criteria determined the ineligible studies: (1) use of vasopressin not during CPR; (2) inappropriate study designs, single-arm trials, observational studies or non-RCTs; (3) case reports or series and narrative and systematic reviews; (4) those with <20 patients; (5) those not reported in the English language; (6) studies with pregnant women or minors.

Search strategy

A systematic search of PubMed, EMBASE, the Cochrane Library and Web of Science was performed from database inception to 15 November 2022 with English language restrictions by two authors (WY and WD). In addition, we conducted a hand search of references obtained from identified studies and known meta-analyses. We combined the following search terms: cardiac arrest, heart arrest, cardiopulmonary resuscitation, advanced cardiovascular life support, ventricle fibrillation, asystole, pulseless electrical activity, ACLS, CPR and vasopressin. The actual search strategy was available in online supplemental file 1.

Data collection and data items

Two authors (WY and XS) separately screened all retrieved citations by reviewing their titles and abstracts. Full-text articles were retrieved if either of the authors considered the abstract potentially suitable. Next, the same authors independently assessed each study's eligibility based on the inclusion criteria. Disagreements were resolved by discussion or consensus with a third author (ZC). Two reviewers (WD and WZ) independently

extracted individual study data using a predefined data extraction form. Any disagreements between review authors were resolved by consultation with a third author (ZC). Data extracted included the name of the first author, date, country, study design, location, sample size, age, sex, rhythm, therapeutic methods in the two groups and outcomes.

Risk of bias in individual studies

Two reviewers evaluated studies for risk of bias using a previously piloted standardised form and the Cochrane Risk of Bias 2 tool¹⁷ for RCTs. The following domains were assessed: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome and bias in the selection of the reported result. The overall risk of bias for each included study was categorised into low risk of bias, some concern of bias or high risk of bias. The risk of publication bias was assessed by visual interpretation of funnel plots if at least 10 studies could be identified reporting the outcome.

Outcomes and subgroups

These outcomes included ROSC, mid-term survival (at hospital discharge, 28 days, 30 days or 1 month) and mid-term good neurological outcome (at hospital discharge, 28 days, 30 days or 1 month). ROSC was defined as spontaneous circulation with no further need for chest compressions sustained for at least 15 min. The good neurological outcome was measured by the Cerebral Performance Category (CPC) or the modified Rankin Scale. The CPC score¹⁸ has five categories as follows: (1) good cerebral performance, (2) moderate cerebral disability, (3) severe cerebral disability, (4) coma or vegetative state, and (5) death. A CPC score of 1–2 is considered a good neurological outcome. The modified Rankin Scale¹⁹ is a 7-point scale, with higher scores indicating worse outcomes. A score of 0–3 was considered a good neurological outcome.

If the information was available, we planned to conduct subgroup analyses of the primary outcome based on: (1) different settings and different study drug strategies (patients with IHCA/OHCA receiving vasopressin only, vasopressin and epinephrine, and VSE); (2) different types of initial rhythm (ventricular fibrillation/tachycardia, asystole and pulseless electrical activity); (3) patients with witnessed arrest; (4) patients with CPR by a bystander; (5) different study qualities (study with low risk of bias, study with some concerns of bias and study with high risk of bias); (6) different study periods (before 2000 and after 2000) and (7) different study regions (North America, Europe and Asia).

Data synthesis

The meta-analysis was conducted using the Review Manager V.5.4 software (RevMan, The Cochrane Collaboration, 2020). Dichotomous data of ROSC, mid-term survival and mid-term good neurological outcome were represented as relative risk (RR) with 95% CIs. A

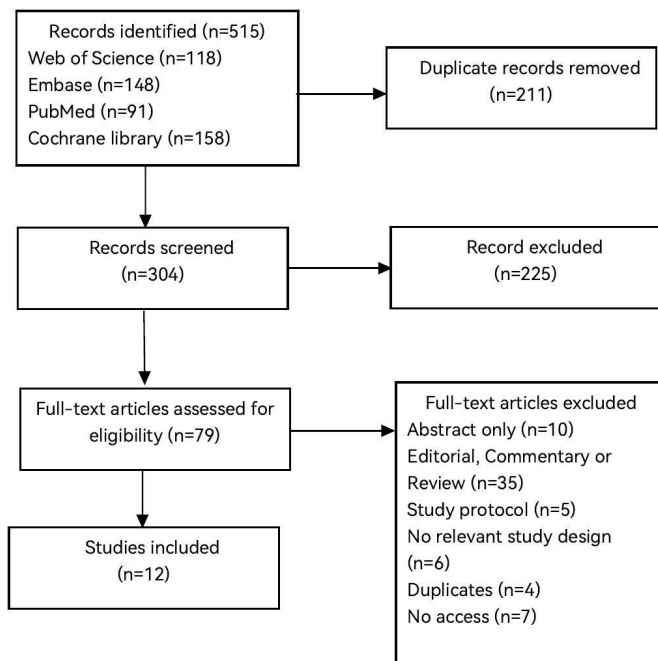


Figure 1 Literature search and study selection flow diagram.

random-effects model was used, and statistical significance was set at $p < 0.05$ for all analyses. Heterogeneity was estimated visually in forest plots and statistically using I^2 tests, as recommended by the Cochrane Collaboration. We considered heterogeneity low if I^2 was $< 25\%$, moderate if $25\% - 50\%$ and substantial if $> 50\%$. To examine heterogeneity, we performed subgroup analysis based on predefined moderator variables, including study region, study quality, age, IHCA versus OHCA and therapeutic methods. The primary outcome estimates for patients with shockable rhythms, with or without arrest witnessed and with or without CPR by a bystander, were also synthesised in the subgroup analysis.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

RESULTS

Study selection and study characteristics

Our search strategy identified 12 randomised trials,^{6 10–14 20–25} including 6718 adult patients who met the eligibility criteria. The flow diagram for study inclusion was shown in figure 1. All included studies were prospective RCTs and included patients between the years 1994⁶ and 2021.¹² Seven trials^{6 11–14 21 23} were performed in Europe, three^{22 24 25} in Asia and two^{10 20} in North America. Eight trials ($n = 5638$) included patients with OHCA^{6 11 20–25} (table 1) and four trials ($n = 1080$) included patients with IHCA^{10 12–14} (table 2). One trial²⁵ did not provide the mean age, and the mean age of patients included in the other 11 trials ranged from 58²³ to 70 years.¹⁰ Four

trials^{6 11 22 24} compared vasopressin with epinephrine in patients with OHCA; four trials^{20 21 23 25} compared epinephrine plus vasopressin with epinephrine and placebo in patients with OHCA (table 1). Three trials^{12–14} compared VSE with epinephrine plus placebo in patients with IHCA; and one trial¹⁰ compared vasopressin with epinephrine in patients with IHCA (table 2). The dosage and course of each trial were presented in tables 1 and 2. In the four trials of IHCA, patients of one trial¹⁰ by Stiehl *et al* received one injection of 40IU of vasopressin, followed by an additional treatment with epinephrine if necessary. Two trials^{13 14} by Mentzelopoulos *et al* in 2009 and 2013 administered hydrocortisone to resuscitated patients with circulatory shock in the intervention arm, whereas the trial¹² by Andersen *et al* did not include any protocolised post-cardiac arrest interventions (table 2).

Risk of bias in studies

The assessment of bias in the RCTs was listed in online supplemental figure 1. Two trials^{14 25} were considered to have a high risk of bias, seven^{6 10 11 20 22–24} were considered to have some concerns for risk of bias and the remaining three^{12 13 21} were considered to have a low risk of bias. The trial²⁵ by Ghafourian *et al* did not report methods of randomisation and minimal baseline characteristics between groups; one²² by Mukoyama *et al* reported limited information on the process of randomisation; and two^{10 24} by Stiehl *et al* and Ong *et al* reported some baseline imbalance between the groups.

The plots for ROSC and mid-term survival were asymmetrical, which strongly imply publication bias (online supplemental figures 2 and 3). Owing to the small number of included studies, a funnel plot did not allow assessment of the publication bias in terms of mid-term good neurological outcome.

Primary outcome

The results of the primary and secondary outcomes are displayed in table 3. Eleven trials^{6 10–14 20–24} with 6607 patients reported the rate of ROSC. When all the trials were pooled, there was no significant difference in patients with ROSC outcome between intravenous vasopressin and placebo (RR: 1.11; 95% CI: 0.99 to 1.26; $I^2 = 62\%$; figure 2). The statistical heterogeneity in this analysis was significant. Subgroup analyses were performed to examine the potential source of heterogeneity (table 3). The setting and different study drug strategies might be the source of heterogeneity.

When analysing the subgroups, including three trials, intravenous VSE in patients with IHCA was associated with significant increase in the rate of ROSC (RR: 1.32; 95% CI: 1.18 to 1.47; $I^2 = 0\%$; figure 2). There was no significant heterogeneity in the results. There were no significant differences in the rate of ROSC in patients with OHCA receiving vasopressin only (RR: 1.03; 95% CI: 0.87 to 1.23; $I^2 = 38\%$; figure 2) and in patients with OHCA receiving vasopressin plus epinephrine (RR: 0.97; 95% CI: 0.87 to 1.08; $I^2 = 0\%$; figure 2). In addition,

Table 1 Characteristics of the studies on out-of-hospital cardiac arrest (OHCA)

Study	Study period/ region	Sample size (study/control)	Inclusion criteria	Baseline characteristics	Treatments	
					Study group	Control group
Lindner <i>et al</i> ⁶	1994–1995 Germany	40 (20/20)	Adults with VF/ VT with OHCA	Mean age: 65 years Male: 72% Initial rhythm: VF/VT 100% Witnessed arrest: 63% Bystander CPR: 63%	1. Vasopressin 40IU IV (CPR cycle 1) 2. If the drug failed to restore spontaneous circulation, resuscitation was continued according to the standard guidelines.	1. Epinephrine 1 mg IV (CPR cycle 1) 2. If the drug failed to restore spontaneous circulation, resuscitation was continued according to the standard guidelines.
Wenzel <i>et al</i> ¹¹	1999–2002 Austria, Germany and Switzerland	1186 (589/597)	Adults with OHCA	Mean age: 66 years Male: 70.3% Initial rhythm: VF/VT 40%, asystole 44%, PEA 16% Witnessed arrest: 78% Bystander CPR: 18%	1. Vasopressin 40IU IV (CPR cycles 1–2) 2. If spontaneous circulation was still not restored, the patient was given an additional injection of epinephrine.	1. Epinephrine 1 mg IV (CPR cycles 1–2) 2. If spontaneous circulation was still not restored, the patient was given an additional injection of epinephrine.
Callaway <i>et al</i> ²⁰	2003–2005 USA	325 (167/158)	Adults with OHCA	Mean age: 66 years Male: 70.0% Initial rhythm: VF/VT 15%, asystole 50%, PEA 23%, other 12% Witnessed arrest: 45% Bystander CPR: 33%	Epinephrine 1 mg+vasopressin 40IU IV (CPR cycle 1)	Epinephrine 1 mg+placebo (CPR cycle 1)
Gueugniaud <i>et al</i> ²¹	2004–2006 France	2894 (1442/1452)	Adults with OHCA	Mean age: 62 years Male: 73% Initial rhythm: VF/VT 9%, asystole 83 %, PEA 8% Witnessed arrest: 75% Bystander CPR: 27%	1. Epinephrine 1 mg+vasopressin 40IU IV (CPR cycles 1–2) 2. If spontaneous circulation was still not restored, the patient was given an additional injection of epinephrine.	1. Epinephrine 1 mg+placebo (CPR cycles 1–2) 2. If spontaneous circulation was still not restored, the patient was given an additional injection of epinephrine.
Mukoyama <i>et al</i> ²²	2001–2006 Japan	336 (178/158)	Adults with OHCA	Mean age: 65 years Male: 71% Initial rhythm: VF/VT 36%, non-VF 64% Witnessed arrest: 44% Bystander CPR: 15%	1. Vasopressin 40 IU IV (the first infection) 2. 40IU of vasopressin IV every 5–10 min 3. Maximum of four injections	1. Epinephrine 1 mg IV (the first infection) 2. 1 mg of epinephrine IV every 5–10 min 3. Maximum of four injections
Ducros <i>et al</i> ²³	2002–2004 France	30 (14/16)	Adults with OHCA	Mean age: 58 years Male: 83% Initial rhythm: VF/VT 7%, asystole 57%, PEA 36% Witnessed arrest: 100% Bystander CPR: 37%	1. Epinephrine 1 mg+vasopressin 40IU IV (T=0 min, T=5 min, T=10 min) 2. After the 15 min study period, all patients still in cardiac arrest received 1 mg of epinephrine every 3 min until ROSC was achieved or ACLS was discontinued.	Epinephrine 1 mg+placebo IV (T=0 min, T=5 min, T=10 min)
Ong <i>et al</i> ²⁴	2006–2009 Singapore	727 (374/353)	Adults with OHCA	Mean age: 64 years Male: 69% Initial rhythm: VF/VT 8%, asystole 19%, PEA 73% Witnessed arrest: 73% Bystander CPR: 15%	1. Vasopressin 40IU IV (CPR cycle 1) 2. If patient remained in cardiac arrest, treatment proceeded according to ACLS guidelines.	1. Epinephrine 1 mg IV (CPR cycle 1) 2. If patient remained in cardiac arrest, treatment proceeded according to ACLS guidelines.
Ghafourian <i>et al</i> ²⁵	2013 Iran	100 (50/50)	Adults with OHCA	Mean age: 30–44 years: 4.5%; 45–59 years: 33.6%; 60–74 years: 44.5%; >75 years: 17.3% Male: 74% Initial rhythm: NR Witnessed arrest: NR Bystander CPR: NR	Vasopressin 20 mg+epinephrine with 40 mg	Epinephrine 1 mg IV

ACLS, Advanced Cardiac Life Support; CPR, cardiopulmonary resuscitation; IV, intravenously; NR, not reported; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF/VT, ventricular fibrillation/ventricular tachycardia.

in the subgroup analyses, there was no significant difference in the rate of ROSC for patients with ventricular fibrillation (RR: 1.02; 95% CI: 0.84 to 1.25; $I^2=30\%$),

asystole (RR: 1.01; 95% CI: 0.90 to 1.14; $I^2=0\%$), pulseless electrical activity (RR: 1.00; 95% CI: 0.82 to 1.21; $I^2=0\%$), witnessed arrest (RR: 1.04; 95% CI: 0.82 to 1.33;

Table 2 Characteristics of the studies on in-hospital cardiac arrest (IHCA)

Study	Study period/ region	Sample size (study/control)	Inclusion criteria	Baseline characteristics	Treatments	
					Study group	Control group
Stiell <i>et al</i> ¹⁰	1997–1998 Canada	200 (104/96)	Adults with IHCA	Mean age: 70 years Male: 63% Initial rhythm: VF/VT 21%, asystole 48%, PEA 30%, other 1%	1. Vasopressin 40IU IV (CPR cycle 1) 2. If the drug failed to restore spontaneous circulation, resuscitation was continued according to the standard guidelines.	1. Epinephrine 1 mg IV (CPR cycle 1) 2. If the drug failed to restore spontaneous circulation, resuscitation was continued according to the standard guidelines.
Mentzelopoulos <i>et al</i> ¹⁴	2006–2007 Greece	100 (48/52)	Adults with IHCA	Mean age: 67 years Male: 60% Initial rhythm: VF/VT 14%, asystole 62%, PEA 25%	1. Epinephrine 1mg+vasopressin 20IU IV (CPR cycles 1–5) 2. Methylprednisolone sodium succinate 40mg IV (first cycle of CPR only) 3. If ROSC but post-resuscitation shock, hydrocortisone 300mg/day IV ≤7 days	1. Epinephrine 1 mg+placebo (normal saline) IV (CPR cycles 1–5) 2. Placebo (normal saline) (first cycle of CPR only) 3. If ROSC but post- resuscitation shock, placebo
Mentzelopoulos <i>et al</i> ¹³	2008–2010 Greece	268 (130/138)	Adults with IHCA	Mean age: 63 years Male: 68% Initial rhythm: VF/VT 17%, asystole 67%, PEA 16%	1. Epinephrine 1 mg+vasopressin 20IU IV (CPR cycles 1–5) 2. Methylprednisolone sodium succinate 40mg IV (first cycle of CPR only) 3. If ROSC but post-resuscitation shock, hydrocortisone 300mg/day IV ≤7 days	1. Epinephrine 1 mg+placebo (normal saline) IV (CPR cycles 1–5) 2. Placebo (normal saline) (first cycle of CPR only) 3. If ROSC but post- resuscitation shock, placebo
Andersen <i>et al</i> ¹²	2018–2021 Denmark	512 (237/264)	Adults with IHCA	Mean age: 70 years Male: 64% Initial rhythm: VF/VT 11%, asystole 35%, PEA 54%	1. Epinephrine 1 mg+vasopressin 20IU IV (CPR cycles 1–5) 2. Methylprednisolone sodium succinate 40mg IV (first cycle of CPR only)	1. Epinephrine 1 mg+placebo (normal saline) IV (CPR cycles 1–5) 2. Placebo (normal saline) (first cycle of CPR only)

CPR, cardiopulmonary resuscitation; IV, intravenously; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF/VT, ventricular fibrillation/ventricular tachycardia.

$I^2=66%$) and CPR by a bystander (RR: 1.22; 95% CI: 0.89 to 1.67; $I^2=38%$).

Secondary outcomes

Mid-term survival

Twelve trials with 6680 patients reported the rate of mid-term survival. Eleven trials^{6 10 11 13 14 20–25} reported the survival rate at hospital discharge, and one trial¹² reported the rate of survival at 30 days. When all the trials were pooled, there was no significant difference in patients with mid-term survival outcome between intravenous vasopressin and placebo (RR: 1.23; 95% CI: 0.90 to 1.66; $I^2=39%$; **figure 3**). In subgroup analyses, including three trials, there was no important difference in the rate of mid-term survival for patients with IHCA who received VSE (RR: 2.15; 95% CI: 0.75 to 6.16; $I^2=76%$; **figure 3**). The test for heterogeneity was significant. After excluding one trial,¹² the heterogeneity decreased significantly (I^2 value from 76% to 0%). Notably, no significant heterogeneity was observed between the two trials,^{13 14} the study protocols were the same and both were reported by the same study group. In addition, there was no significant difference in the rate of mid-term survival for patients with OHCA receiving vasopressin only (RR: 1.14; 95% CI: 0.84 to 1.53; $I^2=0%$; **figure 3**) and in patients with OHCA receiving vasopressin plus epinephrine (RR: 0.86; 95% CI: 0.56 to 1.33; $I^2=0%$; **figure 3**).

Mid-term good neurological outcome

Six trials^{10–14 22} with 2548 patients provided data to evaluate the effect of vasopressin on good neurological outcome.

One trial¹² reported good neurological outcome at 30 days, and the remaining reported good neurological outcome at hospital discharge. There was no significant difference in patients with mid-term good neurological outcome between intravenous vasopressin and placebo (RR: 1.20; 95% CI: 0.77 to 1.87; $I^2=47%$; **figure 4**). For patients with IHCA, patients of three trials^{12–14} receiving VSE did not improve good neurological outcome (RR: 1.80; 95% CI: 0.81 to 4.01; $I^2=56%$; **figure 4**). Statistical heterogeneity in the subgroup was significant. After excluding the 2021 trial,¹² the heterogeneity decreased significantly (I^2 value from 76% to 0%).

DISCUSSION

Our meta-analysis failed to demonstrate benefit from vasopressin with or without epinephrine compared with the standard of care. However, we found that intravenous vasopressin, as part of the VSE during CPR in patients with IHCA, significantly increased the rate of ROSC, but not mid-term survival and mid-term good neurological outcome.

When all the trials were pooled, intravenous vasopressin did not have benefit in patients in cardiac arrest. In a previous trial,⁶ Lindner *et al* found that intravenous vasopressin during CPR significantly increased the benefit for patients with OHCA with ventricular fibrillation. Moreover, one subgroup analysis of an RCT¹⁰ by Stiell *et al* showed that vasopressin was superior to epinephrine in

**Table 3** Data analysis of primary and secondary outcomes

	Outcomes	Trials	Sample size	RR	95% CI	I ² (%)	P value
1	ROSC	11	6607	1.11	0.99 to 1.26	62	0.07
1.1	Subgroup of setting						
	IHCA (VSE)	3	869	1.32	1.18 to 1.47	0	<0.00001
	IHCA (vasopressin only)	1	200	1.09	0.79 to 1.52	–	0.60
	OHCA (vasopressin only)	4	2289	1.03	0.87 to 1.23	38	0.73
	OHCA (vasopressin plus epinephrine)	3	3249	0.97	0.87 to 1.08	0	0.57
1.2	Subgroup of initial rhythm						
	VT/VF	6	1005	1.02	0.84 to 1.25	30	0.81
	PEA	4	627	1.00	0.82 to 1.21	0	0.99
	Asystole	4	3591	1.01	0.90 to 1.14	0	0.81
1.3	Subgroup of patients with witnessed arrest	4	1079	1.14	0.84 to 1.53	66	0.40
1.4	Subgroup of patients with CPR by a bystander	3	771	1.22	0.89 to 1.67	38	0.21
1.5	Subgroup of study quality						
	Low risk	3	3663	1.16	0.93 to 1.43	83	0.18
	Some concerns	7	2844	1.01	0.90 to 1.13	3	0.89
	High risk	1	100	1.08	0.76 to 1.53	–	0.003
1.6	Subgroup of study region						
	North America	2	525	1.06	0.84 to 1.33	0	0.63
	Europe	7	5019	1.15	0.96 to 1.37	77	0.13
	Asia	2	1063	1.06	0.89 to 1.28	0	0.51
2	Mid-term survival	12	6680	1.23	0.91 to 1.66	39	0.18
2.1	Subgroup of setting						
	IHCA (VSE)	3	869	2.15	0.75 to 6.16	76	0.16
	IHCA (vasopressin only)	1	200	0.85	0.41 to 1.78	–	0.67
	OHCA (vasopressin only)	4	2269	1.14	0.84 to 1.53	0	0.40
	OHCA (vasopressin plus epinephrine)	4	3342	0.86	0.56 to 1.33	0	0.50
2.2	Subgroup of initial rhythm						
	VT/VF	5	912	0.87	0.51 to 1.48	35	0.61
	PEA	3	552	0.62	0.16 to 2.39	46	0.48
	Asystole	3	3413	1.29	0.44 to 3.76	57	0.64
2.3	Subgroup of patients with witnessed arrest	4	2117	0.90	0.39 to 2.07	41	0.81
2.4	Subgroup of patients with CPR by a bystander	3	771	1.26	0.64 to 2.46	0	0.51
3	Mid-term good neurological outcome	6	2548	1.20	0.77 to 1.87	47	0.43
3.1	Subgroup of setting						
	IHCA (VSE)	3	869	1.80	0.81 to 4.07	56	0.15
	IHCA (vasopressin only)	1	200	0.71	0.33 to 1.54	–	0.39
	OHCA (vasopressin only)	2	1479	0.94	0.55 to 1.61	13	0.83

CPR, cardiopulmonary resuscitation; IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; RR, relative risk; VF/VT, ventricular fibrillation/ventricular tachycardia; VSE, vasopressin, steroids and epinephrine.

patients with OHCA with asystole, and that the use of vasopressin followed by epinephrine may be more effective than the use of epinephrine alone. However, we found no subgroup differences in patients with ventricular fibrillation, asystole, pulseless electrical activity, witnessed and CPR by a bystander. Our meta-analysis differed from previous trials by Lindner *et al* and Stiell *et al*, which the following possible reasons may explain. First, 5638 patients with OHCA were included, which

contributed to 84% of the study population. For patients with OHCA, an early risk identification, high-quality CPR and emergency medical services (EMS) improved the outcomes among patients in cardiac arrest.²⁶ As shown in table 1, a small number of patients received a bystander CPR in patients with OHCA. All these factors led to the high mortality rate. High mortality may limit the certainty of the evidence for these comparisons. Second, our study included patients from different countries,

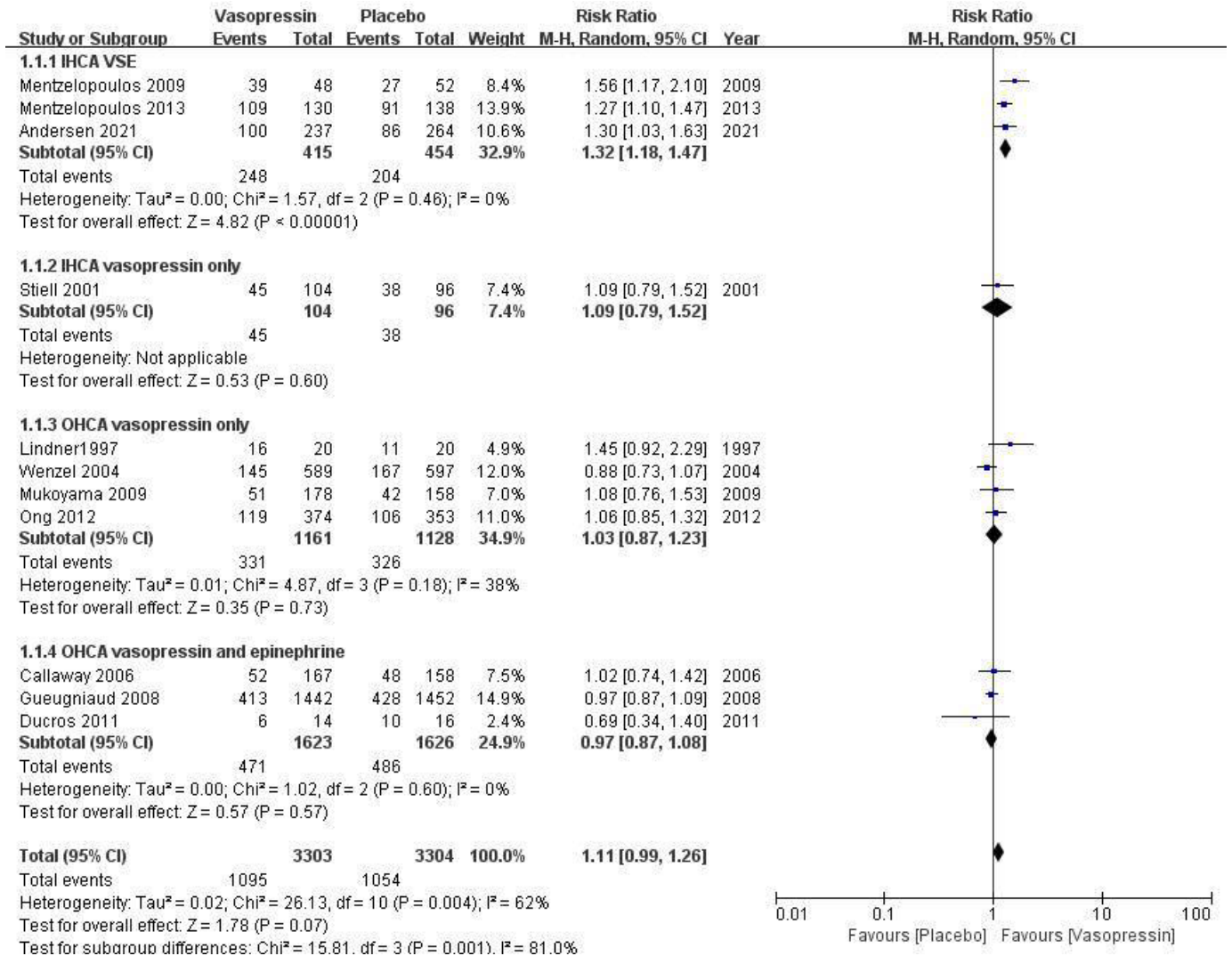


Figure 2 Forest plot of return of spontaneous circulation. IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; VSE, vasopressin, steroids and epinephrine.

and the results could have been affected by the ethnic differences, different resuscitation guidelines and EMS, leading to bias. In our planned subgroup analysis, the outcomes have no significant difference with respect to Europe, Asia and North America. However, the results of a previous meta-analysis²⁷ showed that the combination of vasopressin and epinephrine could improve the ROSC of OHCA in Asia, but patients from other regions did not achieve this result. The main reason for this inconsistency was that we did not include any RCT published in languages other than English. Finally, there was some heterogeneity in dosage and course of vasopressin. Vasopressin is a dose–response drug.¹¹ In our analysis, eight trials of OHCA included four trials of only one dose of vasopressin (40IU), two trials had a maximum of two doses, one trial had a maximum of three doses and one trial had a maximum of four doses (table 1). We could not obtain sufficient data to evaluate the effect of different doses. Inadequate dosing may have contributed to this negative result.

However, using vasopressin is not entirely without benefit. The most significant finding was that vasopressin, as a part of VSE, did improve the rate of ROSC for patients with IHCA but did not improve mid-term survival and mid-term good neurological outcome. The finding was inconsistent with the results of a previous meta-analysis²⁸ that suggested that VSE are associated with improved outcomes in cardiac arrest, including good neurological outcome, survival to hospital discharge and ROSC. A recent study by Granfeldt *et al*²⁹ performed a systematic review and individual participant data meta-analysis of VSE for the treatment of cardiac arrest. A Bayesian framework was used to estimate posterior treatment assuming various prior beliefs. Results favoured vasopressin and glucocorticoids for ROSC but were more uncertain for survival at hospital discharge and favourable neurological outcomes. The conclusion coincides with the results from our study. Moreover, a meta-analysis by Saghaei *et al*³⁰ suggested that VSE combination therapy during and after IHCA may have beneficial effects in terms of the ROSC,

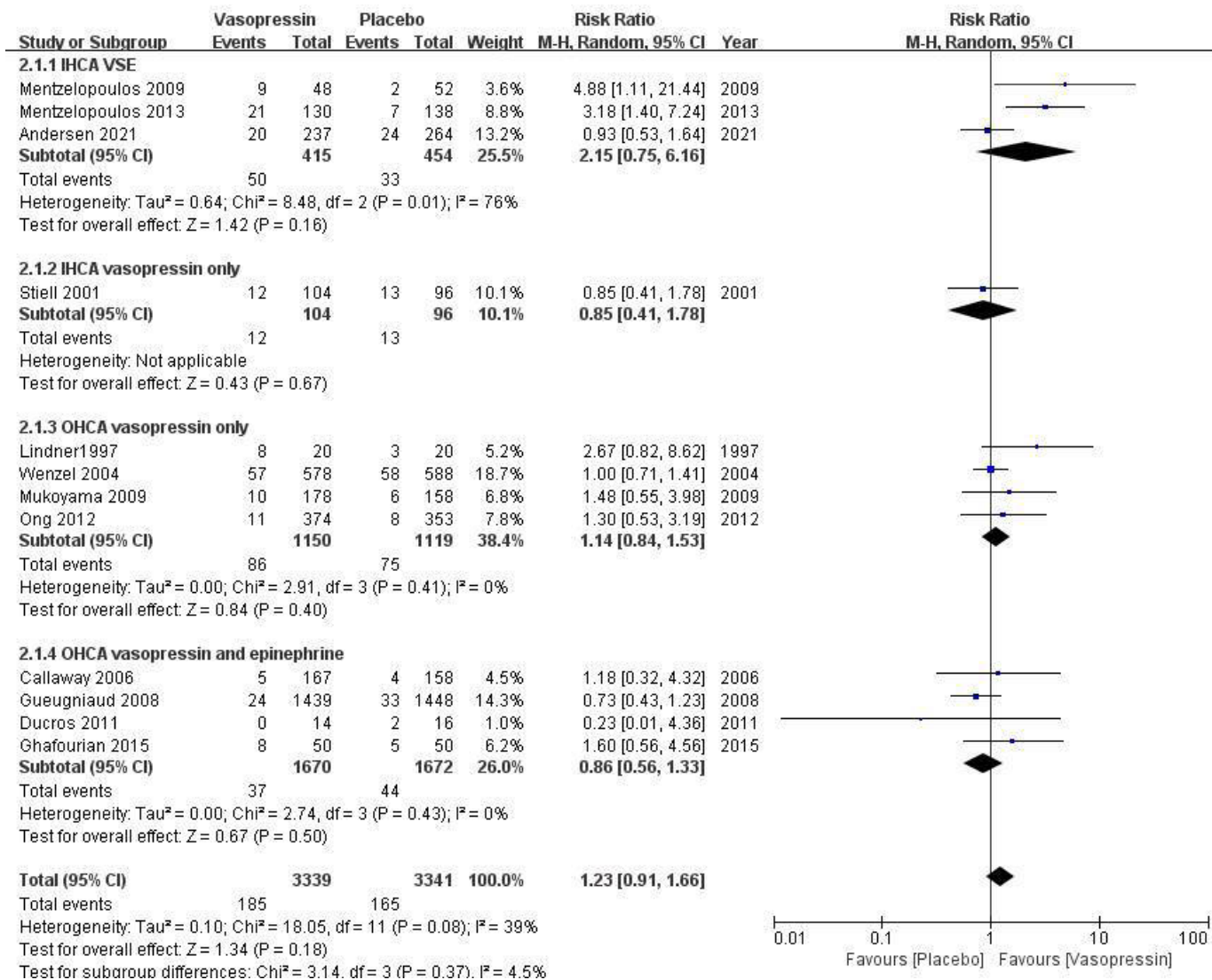


Figure 3 Forest plot of mid-term survival. IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; VSE, vasopressin, steroids and epinephrine.

renal and circulatory failure free days, and mean arterial pressure. In our study, three trials^{12–14} receiving VSE were included, and three trials used the same VSE protocol during CPR, as shown in table 2.

Therefore, vasopressin may improve the rate of ROSC in patients with IHCA. However, we cannot exclude the effects of corticosteroids for mid-term survival and mid-term good neurological outcome. First, the two trials by Mentzelopoulos *et al*^{13 14} that received VSE, using glucocorticoids as an add-on treatment during the post-resuscitation period, showed that VSE could improve mid-term survival and good neurological outcome. However, the Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest (VAM-IHCA) trial¹² did not accept glucocorticoids during the post-resuscitation period and did not achieve better outcomes of mid-term survival and good neurological outcome. The use of glucocorticoids after ROSC could directly improve the outcomes. In addition, in our analysis, the two trials reported survival at hospital discharge and good neurological outcome at

hospital discharge as mid-term outcomes. However, the VAM-IHCA trial reported survival at 30 days and good neurological outcome at 30 days as mid-term outcomes. The two outcome measures may have an effect on the results of mid-term survival and good neurological outcome. It is worth noting that the average dose of vasopressin used in the VAM-IHCA Study was 47IU, while the average dose was 70.3–73.3IU in the studies by Mentzelopoulos *et al* in 2013 and 2009. Therefore, the VAM-IHCA Study provided an insufficient dose of vasopressin in the intervention group.³¹

A difference between our study and those two recent studies^{29 30} by Granfeldt *et al* and Saghafi *et al* is that we evaluated the overall impact of vasopressin in cardiac arrest. There is no single optimal method suitable for all patients. Each regimen is worthy of further exploration. However, the effect of vasopressin only or vasopressin combined with epinephrine is still not conclusive due to limited high-quality data. Current international guidelines^{9 32} do not recommend the use of vasopressin

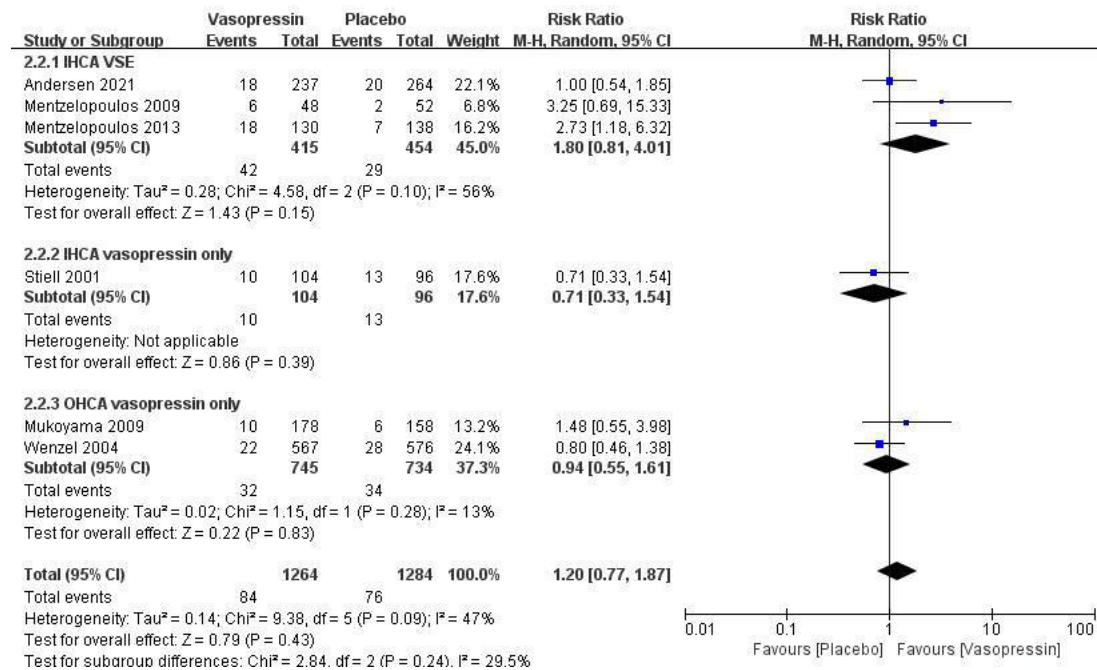


Figure 4 Forest plot of mid-term good neurological outcome. IHCA, in-hospital cardiac arrest; OHCA, out-of-hospital cardiac arrest; VSE, vasopressin, steroids and epinephrine.

as a resuscitation drug for cardiac arrest. We would like to point out that the effect of vasopressin on patients in cardiac arrest cannot be denied. First, the previous trial¹¹ demonstrated that a combination of vasopressin and epinephrine during CPR improves the outcome for patients with OHCA. In vitro studies have indicated that adjuvant therapy with exogenous vasopressin during CPR is more effective than optimal doses of epinephrine in improving blood flow to critical organs.³³ Second, administration of vasopressin and methylprednisolone, compared with placebo, significantly increased the ROSC in IHCA. However, a meta-analysis showed that there was no difference demonstrated in patients with IHCA receiving corticosteroids only or in patients with OHCA receiving corticosteroids only.²⁸ Thus, we did evaluate the effect of three vasopressin regimens, and we did summarise the characteristics of each RCT in tables 1 and 2. We hope that our study can shed some light for future studies. Moreover, patients with OHCA, constituting a significant proportion of the cases treated in the emergency department, were not included in the VSE therapy studies. Therefore, better-designed trials on a large group of patients should be conducted in the future to address the therapeutic effect of vasopressin only, vasopressin combined with epinephrine or VSE on cardiac arrest.

Our systematic review has several limitations. First, there are limited high-quality data to analyse the effect of vasopressin. Nine RCTs contained a high or unclear risk of bias in each domain. Second, data of the included patients were heterogeneous, based on baseline characteristics. The proportion of patients with ventricular fibrillation in each trial was different. Although we performed subgroup analysis of ventricular fibrillation, some trials

did not provide data on outcomes of ventricular fibrillation. Third, despite finding vasopressin as part of VSE that may increase the ROSC, we cannot draw a firm conclusion whether VSE improves mid-term survival or good neurological outcome in patients with IHCA because we cannot exclude the effects of receiving hydrocortisone in resuscitated patients with circulatory shock. Finally, whether the results of this meta-analysis can be generalised to all patients in cardiac arrest remains uncertain. Patients with OHCA, constituting a significant proportion of the study, may influence the generalisability of our results. There are distinct differences in the treatment of patients who experience cardiac arrest in a hospital setting where disease processes, aetiologies and illness severity differ and medical response time is often shorter.²⁶

CONCLUSIONS

Our study failed to demonstrate increased benefit from vasopressin with or without epinephrine compared with the standard of care. However, vasopressin, as a part of VSE, is associated with the improvement of ROSC in patients with IHCA, and the benefit on mid-term survival or mid-term good neurological outcome is uncertain. Better-designed trials on a large group of patients should be conducted in the future to address the therapeutic effect of vasopressin only, vasopressin plus epinephrine or VSE on cardiac arrest.

Contributors WY and XS wrote the draft. WY and XS searched the database. WD and WZ assessed each study eligibility. WY, WZ and WD completed statistical analyses. ZC resolved discordant assessments and conflicting results. ZC conceived the idea and reviewed articles. ZC was guarantor.

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ORCID iDs

Wenqing Yan <http://orcid.org/0000-0003-3980-0868>

Zhi Chen <http://orcid.org/0000-0002-9467-9151>

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