Vasopressors During Cardiopulmonary Resuscitation. A Network Meta-Analysis of Randomized Trials

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Abstract: OBJECTIVES Several randomized controlled trials have compared adrenaline (epinephrine) with alternative therapies in patients with cardiac arrest with conflicting results. Recent observational studies suggest that adrenaline might increase return of spontaneous circulation but worsen neurologic outcome. We systematically compared all the vasopressors tested in randomized controlled trials in adult cardiac arrest patients in order to identify the treatment associated with the highest rate of return of spontaneous circulation, survival, and good neurologic outcome. DESIGN Network meta-analysis. PATIENTS Adult patients undergoing cardiopulmonary resuscitation. INTERVENTIONS PubMed, Embase, BioMed Central, and the Cochrane Central register were searched (up to April 1, 2017). We included all the randomized controlled trials comparing a vasopressor with any other therapy. A network meta-analysis with a frequentist approach was performed to identify the treatment associated with the highest likelihood of survival. MEASUREMENTS AND MAIN RESULTS Twenty-eight studies randomizing 14,848 patients in 12 treatment groups were included. Only a combined treatment with adrenaline, vasopressin, and methylprednisolone was associated with increased likelihood of return of spontaneous circulation and survival with a good neurologic outcome compared with several other comparators, including adrenaline. Adrenaline alone was not associated with any significant difference in mortality and good neurologic outcome compared with any other comparator. CONCLUSIONS In randomized controlled trials assessing vasopressors in adults with cardiac arrest, only a combination of adrenaline, vasopressin, and methylprednisolone was associated with improved survival with a good neurologic outcome compared with any other drug or placebo, particularly in in-hospital cardiac arrest. There was no significant randomized evidence to support neither discourage the use of adrenaline during cardiac arrest.

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Objectives: Several randomized controlled trials have compared adrenaline (epinephrine) with alternative therapies in patients with cardiac arrest with conflicting results. Recent observational studies suggest that adrenaline might increase return of spontaneous circulation but worsen neurologic outcome. We systematically compared all the vasopressors tested in randomized controlled trials in adult cardiac arrest patients in order to identify the treatment associated with the highest rate of return of spontaneous circulation, survival, and good neurologic outcome.

Design: Network meta-analysis.

Patients: Adult patients undergoing cardiopulmonary resuscitation.

Interventions: PubMed, Embase, BioMed Central, and the Cochrane Central register were searched (up to April 1, 2017). We included all the randomized controlled trials comparing a vasopressor with any other therapy. A network meta-analysis with a frequentist approach was performed to identify the treatment associated with the highest likelihood of survival.

Measurements and Main Results: Twenty-eight studies randomizing 14,848 patients in 12 treatment groups were included. Only a combined treatment with adrenaline, vasopressin, and methylprednisolone was associated with increased likelihood of return of spontaneous circulation and survival with a good neurologic outcome compared with several other comparators, including adrenaline. Adrenaline alone was not associated with any significant difference in mortality and good neurologic outcome compared with any other comparator.

Conclusions: In randomized controlled trials assessing vasopressors in adults with cardiac arrest, only a combination of adrenaline, vasopressin, and methylprednisolone was associated with improved survival with a good neurologic outcome compared with any other drug or placebo, particularly in in-hospital cardiac arrest. There was no significant randomized evidence to support neither discourage the use of adrenaline during cardiac arrest. (*Crit Care Med* 2018; 46:e443–e451)

Key Words: adrenaline; cardiac arrest; resuscitation; return of spontaneous circulation; survival; vasopressin

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Cardiac arrest is the most severe medical emergency; despite wide efforts to improve outcome, only a minority of resuscitated patients is discharged in good neurologic condition.

Out-of-hospital cardiac arrest (OHCA) has an estimated occurrence rate of 55–113 cases yearly per 100,000 inhabitants with crude survival rates ranging from 6% to 22% (1–5). In-hospital cardiac arrest (IHCA) has a reported occurrence rate of one to five cases every 1,000 patients (6–8), with survival rates of approximately 24% (9).

Current guidelines on cardiopulmonary resuscitation (CPR) and advanced life support (ALS) recommend the administration of 1 mg of adrenaline (epinephrine) via IV or intraosseous route every 3–5 minutes during resuscitation; however, this recommendation is based on expert opinion, and there is no direct evidence that adrenaline increases survival to hospital discharge (10). In addition, recent observational studies suggest that administration of adrenaline may increase the rate of return of spontaneous circulation (ROSC) but at the cost of a worse neurologic outcome in survivors (11).

Several randomized controlled trials (RCTs) have compared standard adrenaline with higher doses of adrenaline, alternative vasopressors (e.g., vasopressin), combinations of vasopressors, or placebo (12–17), with conflicting results. However, results of these trials have not been compared with each other in order to detect which pharmacologic strategy is the best (18).

A network meta-analysis (NMA) is a statistical technique that allows performing an indirect comparison between treatments that have never been directly compared in randomized clinical trials (19–21).

Therefore, we performed a NMA to indirectly compare and grade all the vasopressor drugs tested in RCTs in adult patients with cardiac arrest in order to identify the treatment associated with the highest survival rate, the highest likelihood of ROSC, and the best neurologic outcome.

MATERIALS AND METHODS

We performed a systematic review and NMA according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (PRISMA-NMA; checklist is available in **Supplemental Digital Content 1**, http://links.lww.com/CCM/D314) (22–25).

Data Sources and Search Strategy

Relevant studies were searched on PubMed, Embase, BioMed Central, and the Cochrane Central register by two independent investigators. Our search strategy aimed to include every RCT investigating the use of a vasopressor agent in adult patients with cardiac arrest. In addition, we employed backward snowballing (i.e., scanning of references of retrieved articles and pertinent reviews) to identify further studies. Literature search was last updated April 1, 2017. The PubMed search strategy, modified from Biondi-Zoccai et al (26), is available in the **supplementary appendix** (Supplemental Digital Content 2, http://links.lww.com/CCM/D315).

Study Selection

Two investigators first examined references at a title/abstract level, and then, if potentially pertinent, retrieved the complete articles. All RCTs on adult patients in cardiac arrest, with at least one group randomized to receive a vasopressor, were considered for inclusion. Exclusion criteria were nonadult population, overlapping population, lack of mortality data, study published as abstract only, and study investigating drugs not available on the market.

Data Extraction and Quality Assessment

Cardiac arrest setting, presentation rhythm, procedural, outcome, and follow-up data were independently abstracted by two investigators. Patients randomized to placebo and those randomized to standard treatment were aggregated together as a single comparison group. After extraction of procedural data from studies comparing low-dose versus high-dose adrenaline (13, 27–34), we decided to define low- and high-dose adrenaline as follows: low-dose adrenaline was less than or equal to 1 mg or 0.02 mg/kg (1.4 mg in a 70 kg person) and high-dose adrenaline was greater than or equal to 2 mg or 0.1 mg/kg. This definition is consistent with results of animal trials performed in the late 80s and early 90s suggesting that adrenaline doses higher than 1 mg might results in improved outcome (35–40). Two independent investigators assessed the internal validity and risk of bias (at a study level) of included trials according to the "Risk of bias assessment tool" developed by The Cochrane collaboration (41), with divergences resolved by consensus.

Data Synthesis and Analysis

Primary outcome was survival at the longest follow-up available, whereas secondary outcomes were ROSC rate and survival with a good neurologic outcome at the longest follow-up available. Good neurologic outcome was defined as per Authors' definition in each study (detailed in **Table 1**). Subgroup analyses included patients with IHCA versus OHCA and patients with shockable versus nonshockable presentation rhythms.

Dichotomous variables were reported as percentages, whereas continuous variables were reported as mean ± SD or median (interquartile range). NMA with a frequentist approach was used to compare mortality at the longest follow-up available between different therapies using the netmeta R package version 8.0 (available at: http://CRAN.R-project.org/package=netmeta) to calculate point estimates of risk differences (RDs) with 95% CIs and generate head-to-head comparison and forest plots using fixed-effects (in case of low heterogeneity/inconsistency) and random-effects models (in case of high heterogeneity/inconsistency) comparing the effect estimates of different therapies relative to low-dose adrenaline (21). P rank scores were generated to determine probability scores to rank which therapies result in the highest survival. Heterogeneity and inconsistency were assessed to generate heat plots, these are a matrix visualization proposed by Krahn et al (56) that highlight hot spots of inconsistency between specific direct evidence in the whole network and allows to highlight possible drivers. Data were analyzed according to the intention-to-treat principle whenever possible. Statistical analysis was performed using R (21, 57–60), with statistical significance for hypothesis testing set at the 0.05 two-tailed level and for heterogeneity testing at the 0.10 two-tailed level.

RESULTS

Study Characteristics

The literature search yielded a total of 372 studies. Of these, 325 were excluded at the title or abstract level because not relevant to the study question or clearly meeting the exclusion criteria (e.g. nonrandomized studies, studies performed in setting other than cardiac arrest, animal studies). A total of 19 studies were then excluded due to prespecified criteria (**Supplementary Table 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315). Finally, 28 studies randomizing 14,848 patients in 12 treatment groups (comparators) were

TABLE 1. Survival With a Good Neurologic Outcome

References	Investigated Treatments	Definition of Good Neurologic Outcome	Treatment 1, Good Outcome/*n*	Treatment 2, Good Outcome/*n*	Treatment 3, Good Outcome/*n*
Brown et al (27)	Low-dose adrenaline vs high-dose adrenaline	CPC score 1–3	24/632	29/648	
Callaham et al (28)	Low-dose adrenaline vs high-dose adrenaline vs noradrenaline	CPC score 1–2	27,260	0/286	0/270
Callaway et al (42)	Low-dose adrenaline vs low-dose adrenaline + vasopressin	N/R	N/R	N/R	
Choux et al (29)	Low-dose adrenaline vs high-dose adrenaline	Glasgow Coma Scale score 9–15	4/265	3/271	
Ducros et al (43)	Low-dose adrenaline vs low-dose adrenaline + vasopressin vs low-dose adrenaline + vasopressin + nitroglycerin	CPC score 1–2	2/16	0/14	0/14
Ghafourian et al (44)	Low-dose adrenaline vs low-dose adrenaline + vasopressin	N/R	N/R	N/R	
Gueugniaud et al (14)	Low-dose adrenaline vs low-dose adrenaline + vasopressin	CPC score 1–2	20/1,452	13/1,442	
Gueugniaud et al (13)	Low-dose adrenaline vs high-dose adrenaline	CPC score 1	26/1,938	26/1,969	
Jacobs et al (17)	Low-dose adrenaline vs placebo	CPC score 1–2	9/272	5/262	
Jaffe et al (45)	Low-dose adrenaline vs low-dose adrenaline + isoproterenol	N/R	N/R	N/R	
Lindner et al (46)	Low-dose adrenaline vs noradrenaline	N/R	N/R	N/R	
Lindner et al (47)	Low-dose adrenaline vs vasopressin	N/R	N/R	N/R	
Lindner et al (30)	Low-dose adrenaline vs high-dose adrenaline	N/R	N/R	N/R	
Lipman et al (31)	Low-dose adrenaline vs high-dose adrenaline	N/R	N/R	N/R	
Mentzelopoulos et al (16)	low-dose adrenaline vs AVM	CPC score 1–2	5/154	11/146	
Mentzelopoulos et al (48)	Low-dose adrenaline vs AVM	CPC score 1–2	2/52	8/48	
Mukoyama et al (49)	Low-dose adrenaline vs vasopressin	CPC score 1–2	6/158	10/178	
Olson et al (50)	Low-dose adrenaline vs methoxamine	N/R	N/R	N/R	
Ong et al (51)	Low-dose adrenaline vs vasopressin	CPC score 1–2	5/353	5/374	
Patrick et al (15)	High-dose adrenaline vs methoxamine	Mean value Glasgow-Pittsburgh Coma Scale	N/R	N/R	
Sherman et al (32)	Low-dose adrenaline vs high-dose adrenaline	CPC score 1–2	0/62	0/78	
Silfvast et al (52)	Low-dose adrenaline vs phenylephrine	N/R	N/R	N/R	
Stiell et al (53)	Low-dose adrenaline vs vasopressin	CPC score 1–2	13/96	10/104	
Stiell et al (33)	Low-dose adrenaline vs high-dose adrenaline	CPC score 1	15/333	9/317	
Turner et al (54)	Low-dose adrenaline vs methoxamine	CPC score 1–2	0/40	0/40	
Weaver et al (55)	Low-dose adrenaline vs lidocaine	N/R	N/R	N/R	
Wenzel et al (12)	Low-dose adrenaline vs vasopressin	CPC score 1–2	28/597	22/589	
Woodhouse et al (34)	High-dose adrenaline vs placebo	CPC score 1–2	0/94	0/100	

AVM = adrenaline-vasopressin-methylprednisolone, CPC = Cerebral Performance Category, N/R = not reported.

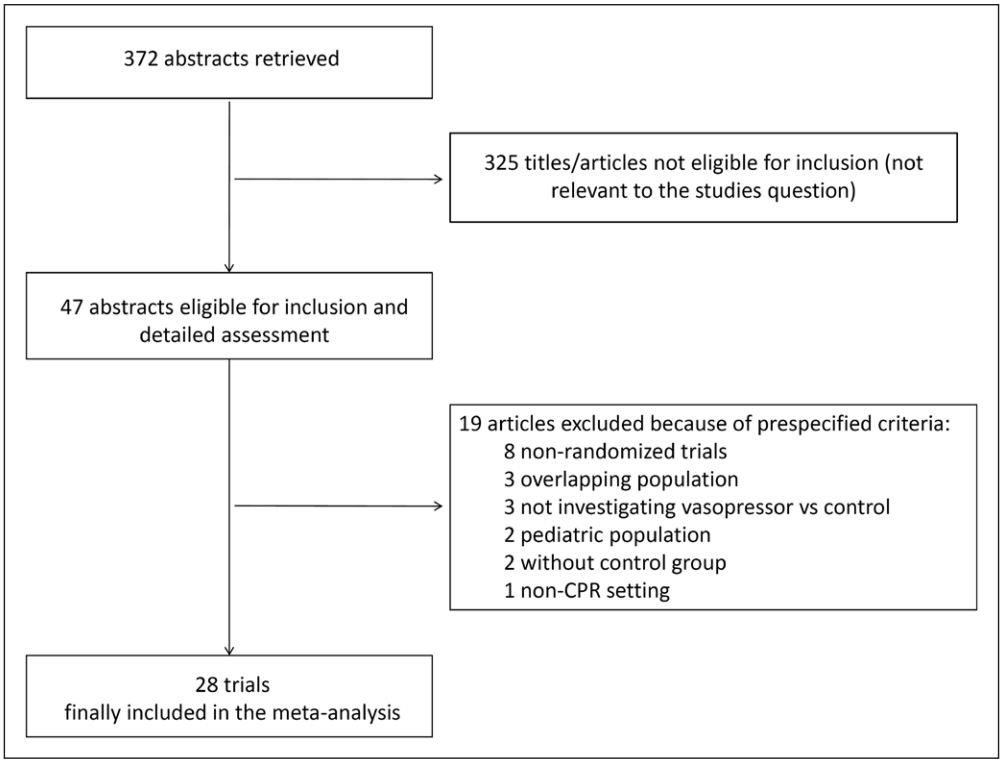

Figure 1. Flow-chart for included studies. CPR = cardiopulmonary resuscitation.

included in the final analysis (flow-chart for trial inclusion is described in **Fig. 1**) (12–17, 27–34, 42–55). The characteristics of included trials are described in **Supplementary Tables 2** and **3** (Supplemental Digital Content 2, http://links.lww.com/CCM/D315).

Twenty-six of 28 the included studies randomized patients into two treatment groups, whereas two studies randomized patients into three treatment groups (28, 43). Thereby, a total of 58 treatment arms were analyzed. The most frequently investigated comparators were low-dose adrenaline (7,211 patients in 26 treatment arms), high-dose adrenaline (3,328 patients in 10 treatment arms), a combination of adrenaline plus vasopressin (1,673 patients in four treatment arms), and a combination treatment of adrenaline, vasopressin, and methylprednisolone (206 patients in two treatment arms). The complete list of treatment arms is reported in Supplementary Tables 2 and 3 (Supplemental Digital Content 2, http://links.lww.com/CCM/D315). Network configuration is presented in **Figure 2**.

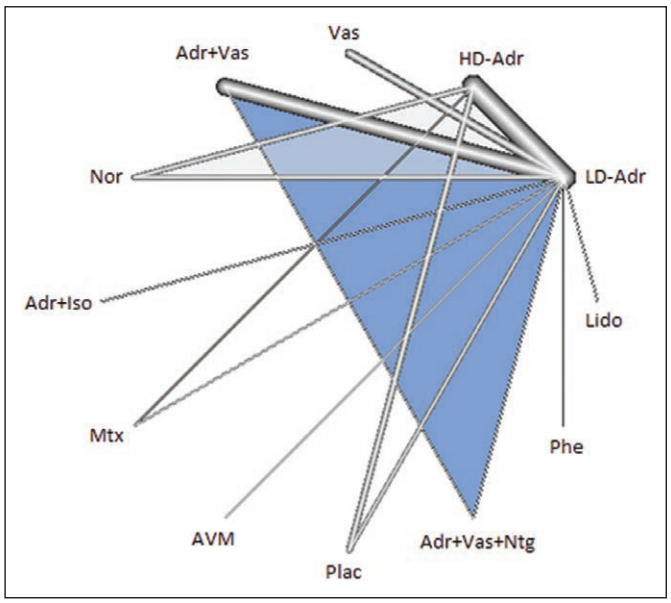

Figure 2. Network configuration. Adr = adrenaline, AVM = adrenaline + vasopressin + methylprednisolone, HD = high dose, Iso = isoproterenol, LD = low dose, Lido = lidocaine, Mtx = methoxamine, Nor = noradrenaline, Ntg = nitroglycerin, Phe = phenylephrine, Plac = placebo, Vas = vasopressin.

Seven studies were judged to be at low risk of bias (12, 16, 31, 42, 47, 48, 53), 10 studies at unclear risk of bias (13, 14, 17, 30–32, 42, 49, 50, 53), and 11 studies at high risk of bias (15, 27–29, 34, 44–46, 49, 52, 55) (**Supplementary Table 4**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315).

Quantitative Data Synthesis

Overall Survival. Among the 12 treatments analyzed, the combination of adrenaline, vasopressin and methylprednisolone (16, 41) was associated with increased likelihood of survival as compared with low-dose adrenaline (RD vs low-dose adrenaline, 0.06; 95% CI, 0.01–0.11) (**Supplementary Table 5**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315; and **Supplementary Fig. 1**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315). Rank analysis showed that this combination had the highest probability to be the best treatment in terms of survival, followed by noradrenaline (norepinephrine), vasopressin, phenylephrine and low-dose adrenaline (**Table 2**).

Network head-to-head comparison showed that the combination of adrenaline, vasopressin and methylprednisolone (16, 41) was associated with an increased survival when compared also to high-dose adrenaline, vasopressin, the combination of adrenaline-vasopressin, methoxamine, and placebo (Supplementary Table 5, Supplemental Digital Content 2, http://links.lww.com/CCM/D315). Heterogeneity among studies was low ($tau^2 < 0.0001$; $I^2 = 0\%$; Q statistics $p = 0.50$). Heat plot is presented in **Supplementary Figure 8** (Supplemental Digital Content 2, http://links.lww.com/CCM/D315).

ROSC. Rank analysis showed that adrenaline-vasopressin-methylprednisolone had the highest probability to be the best

TABLE 2. Network Meta-Analysis Ranking of Treatments

Rank	Treatment	Probability to Be the Best
1	Adrenaline + vasopressin + methylprednisolone	0.93
2	Noradrenaline	0.71
3	Vasopressin	0.63
4	Phenylephrine	0.62
5	Adrenaline—low dose	0.55
6	Lidocaine	0.53
7	Adrenaline—high dose	0.49
8	Placebo	0.36
9	Adrenaline + isoproterenol	0.35
10	Adrenaline + vasopressin	0.35
11	Adrenaline + vasopressin + nitroglycerin	0.31
12	Methoxamine	0.16

Treatments with highest ranking have the highest probability to be the best in terms of survival.

pharmacologic treatment, followed by noradrenaline and high-dose adrenaline, phenylephrine, and vasopressin.

Head-to-head comparison showed an increased probability of ROSC with adrenaline-vasopressin-methylprednisolone compared with high-dose adrenaline, vasopressin, adrenaline-vasopressin, methoxamine, and placebo. Conversely, methoxamine reduced ROSC probability compared with high-dose adrenaline, vasopressin, and noradrenaline (**Supplementary Tables 6** and **11**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315; and **Supplementary Fig. 2**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315). Heterogeneity among studies was high ($tau^2 = 0.0025$; $I^2 = 61.4\%$; Q statistics $p = 0.0003$).

Good Neurologic Outcome. Using low-dose adrenaline as reference, only the combination of adrenaline, vasopressin, and methylprednisolone was associated with increased survival with a good neurologic outcome (RD vs low-dose adrenaline, 0.06; 95% CI, 0.01–0.10). Head-to-head network comparison showed increased survival with good neurologic outcome when adrenaline-vasopressin-methylprednisolone was compared with high-dose adrenaline, vasopressin, adrenaline-vasopressin, noradrenaline, and placebo (**Supplementary Tables 7** and **12**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315; and **Supplementary Fig. 3**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315). Heterogeneity among studies was low ($tau^2 < 0.0001$; $I^2 = 0\%$; Q statistics $p = 0.69$).

IHCA and OHCA. When analyzing studies investigating OHCA, no treatment was associated with increased survival compared with others (**Supplementary Tables 10** and **15**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315; and **Supplementary Fig. 6**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315). Heterogeneity among studies was low ($tau^2 < 0.0001$; $I^2 = 0\%$; Q statistics $p = 0.50$).

Considering IHCA, the combination of adrenaline, vasopressin, and methylprednisolone was associated with increased survival compared with low-dose adrenaline (RD, 0.06; 95% CI, 0.01–0.11). Head-to-head comparison showed increased survival associated with adrenaline-vasopressin-methylprednisolone treatment when compared with high-dose adrenaline (RD, 0.07; 95% CI, 0.01–0.14) (**Supplementary Tables** 11 and **16**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315; and **Supplementary Fig. 7**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315). Heterogeneity among studies was moderate ($tau^2 = 0.0012$; $I^2 = 30.5\%$; Q statistics $p = 0.23$).

Outcomes According to Initial Rhythm. When analyzing treatments for cardiac arrest with an initial shockable rhythm, we found that no treatment was superior to another in terms of survival. Heterogeneity among studies was low ($tau^2 = 0.0003$; $I^2 = 12.8\%$; Q statistics $p = 0.33$) (**Supplementary Tables 8** and **13**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315; and **Supplementary Fig. 4**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315).

Similarly, no treatment was associated with increased survival when analyzing data on cardiac arrest with a nonshockable rhythm at presentation (**Supplementary Tables 9** and **14**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315; and **Supplementary Fig. 5**, Supplemental Digital Content 2, http://links.lww.com/CCM/D315). Heterogeneity among studies was low ($tau^2 < 0.0001$; $I^2 = 0\%$; Q statistics $p = 0.60$).

DISCUSSION

In this large NMA of randomized trials investigating vasopressors during CPR, we found that only a combined treatment with adrenaline, vasopressin, and methylprednisolone (16, 48) was associated with a significantly higher likelihood of ROSC, survival, and good neurologic outcome compared with low-dose adrenaline and to several other comparators. Conversely, methoxamine, an α_1-adrenergic agonist (61), was associated with reduced likelihood of ROSC. Considering IHCA, the combined treatment with adrenaline, vasopressin, and methylprednisolone was once again the only treatment associated with increased survival; on the other hand, in OHCA, no treatment was found to be superior over the others.

Compared with previous systematic reviews and meta-analyses published on the topic (62–67), this is the first study to compare and grade using a statistical analysis of the efficacy of all vasopressors tested during CPR in RCTs. In contrast, previous meta-analyses focused on single agents, usually adrenaline (63, 65, 66) or vasopressin (64, 67). The most comprehensive systematic (but not quantitative) review published so far by Larabee et al [62] in 2012 concluded that 1) adrenaline (both a low-dose and high-dose) provide a short-term benefit in terms of ROSC, 2) there are insufficient evidences to support or discourage vasopressin use, and 3) noradrenaline may provide superior results in terms of ROSC compared with adrenaline.

A major difference with our study is that Larabee et al (62) did not perform a statistical analysis of their results.

The most widely investigated alternative to adrenaline has been vasopressin. Current evidence concerning vasopressin use in cardiac arrest shows no survival benefit in unselected patients. A meta-analysis by Mentzelopoulos et al (67) published in 2012 showed that vasopressin versus control was associated with higher long-term survival only in patients with asystole, especially when the drug was administered within 20 minutes from arrest. In 2014, a meta-analysis from Layek et al (64) showed that vasopressin was associated with an increased likelihood of ROSC when the drug was used in the setting of IHCA and an increased likelihood of survival to hospital discharge and survival with a favorable neurologic outcome when vasopressin was administered as "repeated boluses of 4–5 times titrated to the desired effects." We found no significant increase in the rate of ROSC or survival to the longest follow-up available when vasopressin was used compared with other agents. The most likely explanation for these differences is that results of the meta-analysis by Layek et al (64) are significantly influenced by the two studies performed by Mentzelopoulos et al (16, 48), which were analyzed together with studies on vasopressin. In contrast, in our study, we grouped these two RCTs separately since the administration of vasopressin was combined to adrenaline and methylprednisolone, and the study design also included a postresuscitation treatment.

In their meta-analysis of RCTs and observational trials on adrenaline use during CPR, Patanwala et al (65) found that adrenaline was associated with decreased survival after cardiac arrest. However, their analysis included observational studies, subjected to higher risk of bias than RCTs, that mainly influenced the results. Differently from that study, we included only RCTs.

In our study, we were able to identify a treatment that, compared with all other vasopressors administered during CPR ever tested in RCTs, was shown to increase survival with a good neurologic outcome. Differently from previous literature, our results are for the first time supported by a statistical approach indirectly comparing the efficacy of all treatments ever assessed in RCTs. However, we acknowledge that these results are mainly driven by two studies by Mentzelopoulos et al (16), which were performed in the setting of IHCA, with a relevant proportion of patients being already in an ICU, where all equipment for ALS and postresuscitation care are readily available, and the staff is well trained in the management of cardiac arrest. Another possible explanation for the positive results obtained by Mentzelopoulos et al (16) is the effect of steroids on postresuscitation syndrome. Steroids administration could attenuate postarrest systemic inflammatory response syndrome (68, 69). In addition, release of adrenal hormone is frequently impaired after cardiac arrest, which reduces the physiologic stress response (70, 71). Finally, steroids may increase response to vasopressors due to their effect on intracellular signaling pathways (72). Notably, the protocol investigated by Mentzelopoulos et al (16) does not allow to distinguish between effects of steroids administration during versus after CPR, as patients in the treatment groups received steroids in both phases. Nevertheless, a recent multicenter RCT enrolling patients with refractory shock following cardiac arrest showed no difference in terms of shock reversal, good neurologic outcome, or survival to discharge between patients receiving hydrocortisone or placebo (73). These results suggest that the positive effects found by Mentzelopoulos et al (16) may derive from vasopressin and methylprednisolone administration during CPR, rather than hydrocortisone administration after resuscitation.

Current ALS guidelines recommend administration of 1 mg adrenaline during CPR (10). This recommendation is based on low quality of evidence, in particular on old, nonrandomized trials, and has been part of resuscitation guidelines for decades (74). Although in our study we found that only adrenaline-vasopressin-methylprednisolone combination was associated with increased survival, results of ranking analysis provide some interesting clues. Low-dose adrenaline was ranked only fifth, behind adrenaline-vasopressin-methylprednisolone, noradrenaline, and phenylephrine, whereas the combination adrenaline-vasopressin was ranked only tenth. This suggests that the two most widely used and investigated vasopressors or combination of vasopressors may not necessarily be the most effective in terms of potential impact on survival.

Interestingly, adrenaline (a potent β- and α-adrenergic agonist) was ranked below noradrenaline (which has higher affinity for α-adrenergic receptors than for β-receptors) and phenylephrine (a pure α-adrenergic agonist). Currently, several nonrandomized studies have questioned the benefit of adrenaline administration during CPR with worse neurologic outcome in patients receiving adrenaline, even in the face of an increased ROSC (11, 75–78). This has been explained by some authors with a detrimental effect of β-adrenergic stimulation on postresuscitation myocardial function and cerebral perfusion during CPR (79–81). However, other studies did not confirm these findings (82, 83), and a small study showed increased cerebral oxygenation following adrenaline administration (84). In our study, we found no evidence of worse outcome associated with either high- or low-dose adrenaline. However, it should be noted that most of the studies compared adrenaline with another vasopressor, and use of open-label, low-dose adrenaline was generally allowed at some point of CPR algorithm in most of the studies. An ongoing randomized trial will hopefully provide a definitive answer on the role of prehospital adrenaline administration (Pre-hospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of drug administration in Cardiac arrest [PARAMEDIC-2]: [ISRCTN73485024]) (85).

Nevertheless, in absence of adequately powered and high-quality RCTs, we believe that clinicians should follow current international guidelines provided by professional societies (10, 86), although application of the adrenaline-vasopressin–methylprednisolone protocol might be considered in the ICU setting. External validity and reproducibility of positive results obtained by Mentzelopoulos et al (16) and feasibility of their protocol outside the ICU should be confirmed in additional pragmatic international mRCTs, before widespread use could be recommended (87, 88).

A strength of our study is that we systematically searched and included only RCTs performed on this topic. In contrast to previous reviews and meta-analyses, our network meta-analytic statistical approach allowed us to indirectly compare all the vasopressors used in RCT among each other.

Our study has some limitations. First, we included studies performed in both OHCA and IHCA settings. However, we performed specific subgroup analyses for the different settings showing that the positive results of a combined treatment of vasopressin, adrenaline, and methylprednisolone arise from two studies performed by Mentzelopoulos et al in IHCA. Second, the quality of included trials was heterogeneous, with the majority of trials carrying an unclear or a high risk of bias. Our analysis focusing on ROSC highlighted a high heterogeneity between studies, which limits the validity of this specific analysis. We hypothesize that heterogeneity is most likely due to case mix, ancillary treatments, and possibly different ROSC definitions. However, we believe that this secondary analysis provides interesting clues to support future investigations on the most effective treatments. The definition of good neurologic outcome is not consistent across all included studies, although all but two define good neurologic outcome as Cerebral Performance Category score 1 or 2, in line with current recommendations (89). Finally, all limitations of meta-analyses apply also to network meta-analyses (20, 23, 90). In particular, meta-analyses should be considered hypothesis generating, particularly when available trials are heterogeneous or with high risk of bias.

CONCLUSIONS

This NMA of RCTs found that only a combined treatment with adrenaline, vasopressin, and methylprednisolone was associated with improved survival with a good neurologic outcome and ROSC probability compared with several other comparators, including adrenaline, particularly in IHCA. No significant randomized evidences support neither discourage the use of adrenaline during cardiac arrest. High-quality studies are needed to confirm these findings and explore further therapeutic treatments in this setting.

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