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Effect of Vasopressin and Methylprednisolone vs Placebo on Return of Spontaneous Circulation in Patients With In-Hospital Cardiac Arrest
A Randomized Clinical Trial

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IMPORTANCE Previous trials have suggested that vasopressin and methylprednisolone administered during in-hospital cardiac arrest might improve outcomes.

OBJECTIVE To determine whether the combination of vasopressin and methylprednisolone administered during in-hospital cardiac arrest improves return of spontaneous circulation.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, double-blind, placebo-controlled trial conducted at 10 hospitals in Denmark. A total of 512 adult patients with in-hospital cardiac arrest were included between October 15, 2018, and January 21, 2021. The last 90-day follow-up was on April 21, 2021.

INTERVENTION Patients were randomized to receive a combination of vasopressin and methylprednisolone (n = 245) or placebo (n = 267). The first dose of vasopressin (20 IU) and methylprednisolone (40 mg), or corresponding placebo, was administered after the first dose of epinephrine. Additional doses of vasopressin or corresponding placebo were administered after each additional dose of epinephrine for a maximum of 4 doses.

MAIN OUTCOMES AND MEASURES The primary outcome was return of spontaneous circulation. Secondary outcomes included survival and favorable neurologic outcome at 30 days (Cerebral Performance Category score of 1 or 2).

RESULTS Among 512 patients who were randomized, 501 met all inclusion and no exclusion criteria and were included in the analysis (mean [SD] age, 71 [13] years; 322 men [64%]). One hundred of 237 patients (42%) in the vasopressin and methylprednisolone group and 86 of 264 patients (33%) in the placebo group achieved return of spontaneous circulation (risk ratio, 1.30 [95% CI, 1.03-1.63]; risk difference, 9.6% [95% CI, 1.1%-18.0%]; $P = .03$). At 30 days, 23 patients (9.7%) in the intervention group and 31 patients (12%) in the placebo group were alive (risk ratio, 0.83 [95% CI, 0.50-1.37]; risk difference: −2.0% [95% CI, −7.5% to 3.5%]; $P = .48$). A favorable neurologic outcome was observed in 18 patients (7.6%) in the intervention group and 20 patients (7.6%) in the placebo group at 30 days (risk ratio, 1.00 [95% CI, 0.55-1.83]; risk difference, 0.0% [95% CI, −4.7% to 4.9%]; $P > .99$). In patients with return of spontaneous circulation, hyperglycemia occurred in 77 (77%) in the intervention group and 63 (73%) in the placebo group. Hypernatremia occurred in 28 (28%) and 27 (31%), in the intervention and placebo groups, respectively.

CONCLUSIONS AND RELEVANCE Among patients with in-hospital cardiac arrest, administration of vasopressin and methylprednisolone, compared with placebo, significantly increased the likelihood of return of spontaneous circulation. However, there is uncertainty whether this treatment results in benefit or harm for long-term survival.

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In-hospital cardiac arrest occurs in approximately 2000 patients each year in Denmark and 300 000 patients each year in the United States.[1,2] Outcomes remain poor, with only approximately 25% surviving to hospital discharge in 2017 in the United States.[3] Despite this low survival, there has been limited research focused on improving outcomes for this patient population.[3]

Similar to the out-of-hospital setting, treatment of in-hospital cardiac arrest focuses on early recognition, basic life support (eg, chest compressions and ventilations), advanced life support (eg, defibrillation and drugs), and subsequent post-cardiac arrest care. Most recommendations for treatment of in-hospital cardiac arrest are extrapolated from the out-of-hospital setting. Drugs currently used during in-hospital cardiac arrest, when appropriate, includes epinephrine and amiodarone or lidocaine.[4,5]

In 2 randomized, double-blind trials, published in 2009 and 2013, Mentzelopoulos et al[6,7] compared the addition of vasopressin (20 IU for each dose of epinephrine) and 1 dose of glucocorticoids (40 mg of methylprednisolone) during cardiac arrest with placebo. Both trials, which had a combined sample size of 368 patients, showed a large improvement in outcomes.[6,7] For example, the most recent and largest of the trials found that survival with a favorable neurologic outcome occurred in 18 of 130 patients (14%) in the intervention group compared with 7 of 138 patients (5%) in the placebo group, a finding that was statistically significant.[7] Despite these findings, the current United States and European guidelines[8,9] for treatment of cardiac arrest do not recommend the use of vasopressin and glucocorticoids, reflecting lack of clinical trial data that confirmed the findings of Mentzelopoulos et al.

The Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest (VAM-IHCA) trial was designed to test whether vasopressin and glucocorticoids can improve return of spontaneous circulation for patients with in-hospital cardiac arrest.

Key Points

Question Does the combination of vasopressin and methylprednisolone administered during in-hospital cardiac arrest improve return of spontaneous circulation?

Findings In this randomized trial that included 501 patients with in-hospital cardiac arrest in Denmark, the proportion of patients who achieved return of spontaneous circulation was 42% in the vasopressin and methylprednisolone group and 33% in the placebo group, a difference that was statistically significant.

Meaning Among patients with in-hospital cardiac arrest, administration of vasopressin and methylprednisolone compared with placebo significantly increased the likelihood of return of spontaneous circulation, but it is uncertain whether there is benefit or harm for long-term survival.

Methods

Trial Design and Oversight

This trial was an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group, double-blind, superiority trial of vasopressin and methylprednisolone during adult in-hospital cardiac arrest.[10] The protocol, which is provided in Supplement 1, was written by the steering committee and approved by the regional ethics committee and the Danish Medicines Agency. Minor differences between the article and the protocol are described in eAppendix 1 in Supplement 2. An independent data monitoring committee oversaw the trial. Oral and subsequent written informed consent was temporarily obtained from a physician independent of the trial until the patient regained capacity or a surrogate became available according to Danish legislation (additional details are provided in the protocol in Supplement 1). Patients or surrogates provided consent for all patients who survived.

Patients

Patients were included from 10 hospitals in Denmark, including 4 large university hospitals. Adult patients (age ≥18 years) were eligible for the trial if they had an in-hospital cardiac arrest and received at least 1 dose of epinephrine during the cardiac arrest. Patients with a cardiac arrest that started outside the hospital were not included. Exclusion criteria included a clearly documented do-not-resuscitate order prior to the cardiac arrest, prior enrollment in the trial, invasive mechanical circulatory support (extracorporeal circulation or left ventricular assist device) at the time of the cardiac arrest, and known or suspected pregnancy at the time of the cardiac arrest.

Randomization

The study kits, and therefore the patients, were randomized in a 1:1 ratio via a random number generator to either vasopressin and methylprednisolone or placebo in blocks with random sizes of 2, 4, or 6. The randomization was stratified according to site.

Intervention

The trial drugs consisted of 40 mg of methylprednisolone (Solu-Medrol, Pfizer) and 20 IU of vasopressin (Empressin, Amomed Pharma GmbH) given as soon as possible after the first dose of epinephrine. Additional doses of vasopressin (20 IU) were administered after each epinephrine dose for a maximum of 4 doses (80 IU). Placebo consisted of 9 mg/mL of sodium chloride from identical ampoules. The trial drugs were placed in a blinded study kit, which was brought to the cardiac arrest by a dedicated member of the clinical cardiac arrest team. The trial was double-blind, with patients, investigators, clinicians, and outcome assessors unaware of the allocated treatment.

Outcomes

The primary outcome was return of spontaneous circulation, which was defined as spontaneous circulation with no further need for chest compressions sustained for at least 20 minutes.[11]

Key secondary outcomes included survival at 30 days and survival at 30 days with a favorable neurologic outcome, which was defined as a Cerebral Performance Category score of 1 or 2. The Cerebral Performance Category score is a 5-point scale assessing neurologic outcomes after brain damage, with higher scores indicating worse outcomes.[12] Additional outcomes, as described below, were considered tertiary outcomes.

Neurologic outcome was also assessed using the modified Rankin Scale, which is a 7-point scale, with higher scores indicating worse outcomes.[13] A score of 0 to 3 was considered a favorable outcome. At 30 days, health-related quality of life was assessed using the EuroQol 5 Dimension 5 Level (EQ-5D-5L) and indexed based on Danish data.[14,15] The results from the EQ-5D-5L are reported both as the numeric value directly assessed by the patient and as the indexed value. The numeric value is reported on a scale from 0 to 100, with higher scores indicating a better health-related quality of life, while the indexed value can also be negative. Outcomes were assessed in person if the patient was still in the hospital and otherwise by a telephone interview. If the patient was not able to participate, a relative or clinical personnel provided the assessment. Similar outcomes were assessed at 90 days, 180 days, and 1 year. Results for the 30- and 90-day follow-up are provided here, while data on longer-term outcomes are still being collected.

As a measure of organ dysfunction after return of spontaneous circulation, we collected data on the Sequential Organ Failure Assessment (SOFA) score at 24, 48, and 72 hours after the cardiac arrest as well as vasopressor- and ventilator-free days within the first 14 days. The SOFA score ranges from 0 to 24, with higher scores indicating worse organ dysfunction.[16] Predefined potential adverse events, including hyperglycemia, hypernatremia, infections, gastrointestinal bleeding, and mesenteric and peripheral ischemia, were also collected, with a full list and definitions provided in the protocol in Supplement 1.

Sample Size Calculation

The sample size was based on the primary outcome of return of spontaneous circulation. Based on unpublished preliminary data from the participating hospitals, we assumed that 45% of patients in the placebo group would achieve return of spontaneous circulation. We assumed an absolute difference of 13% between the placebo and intervention group, corresponding to 58% of patients achieving return of spontaneous circulation in the intervention group. This effect estimate is consistent with the Mentzelopoulos et al[6,7] trials. With these estimates, an α of .05, and the use of the χ^2 test, a total of 492 patients were required to have 80% power to detect a statistically significant difference between groups.

Statistical Analysis

Patients were analyzed according to their randomized assignment. The analyses only included patients receiving the first dose of either of the trial drugs and meeting all inclusion criteria and no exclusion criteria.[17]

Binary data are presented as counts and percentages, and differences between groups are presented as both risk differences and risk ratios with 95% CIs. CIs were estimated using the method described by Miettinen and Nurmimen.[18] Continuous data are presented as means with SDs or medians with first and third quartiles, depending on the distribution of the data. Differences between groups in continuous outcomes are presented as mean differences with 95% CIs obtained from generalized linear models with robust errors. As a sensitivity analysis, the risk ratio for the primary outcome was estimated while adjusting for site and strong prognostic factors, specifically age, whether the cardiac arrest was witnessed, and the initial rhythm, as covariates.[19,20] Modified Poisson regression was used for this analysis.[21]

Two-sided *P* values, obtained from Fisher exact test, are reported for the primary and key secondary outcomes. A *P* value of less than .05 was considered significant. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary outcomes should be interpreted as exploratory. Five subgroup analyses, all prespecified in the protocol, were performed according to the first documented rhythm, witnessed status, patient age, time from cardiac arrest to trial drug administration, and time from epinephrine administration to administration of the trial drug.

All analyses were performed in SAS version 9.4 (SAS Institute).

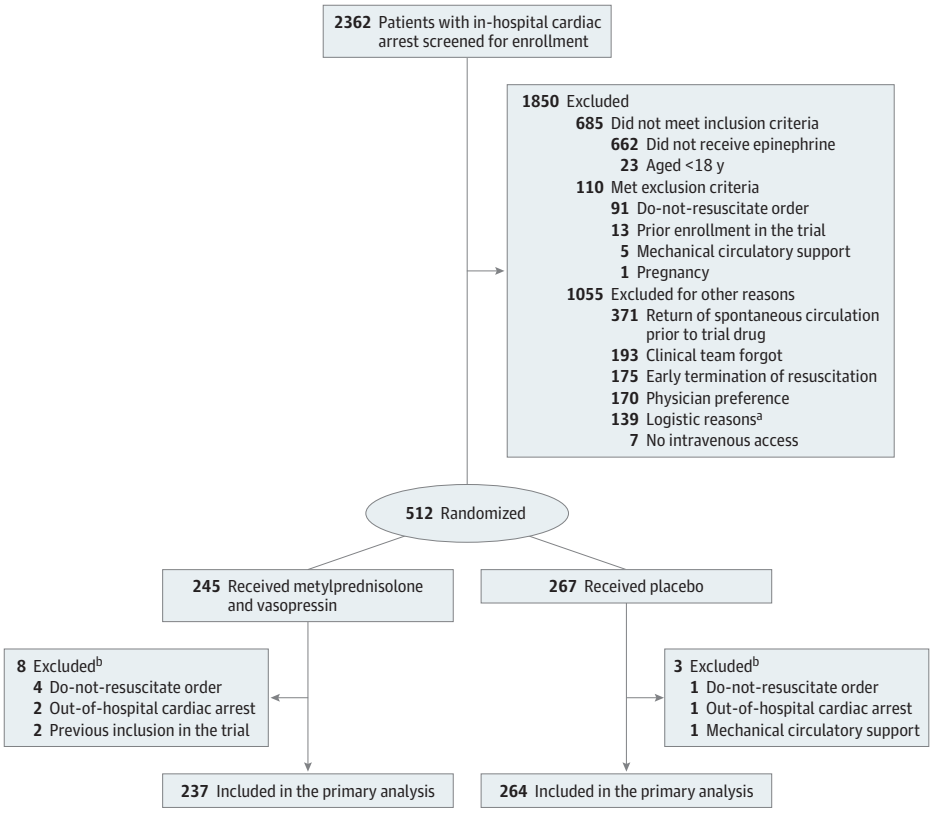
Results

Patient Characteristics

From October 15, 2018, to January 21, 2021, 512 patients were randomized and received the trial drugs (**Figure 1**; eTable 1 in Supplement 2), with the last 90-day follow-up occurring on April 21, 2021. Eleven patients were excluded because they did not meet all inclusion criteria or met at least 1 exclusion criterion, leaving 501 patients for the analysis (237 in the intervention group and 264 in the placebo group). There was no loss to follow-up.

Baseline characteristics were similar between the 2 groups (**Table 1**; eTable 2 in Supplement 2). The mean (SD) age was 71 (13) years and 322 (64%) were men. Most of the cardiac arrests (66%) occurred among patients who were receiving care in standard medical or surgical units and presented with an initial nonshockable rhythm (90%). The median time from the cardiac arrest to epinephrine and trial drug administration was 5 minutes (first and third quartiles: 3, 8) and 8 minutes (first and third quartiles: 6, 12), respectively. Non-trial-related interventions during and after the cardiac arrest were generally similar between groups (eTables 3 and 4 in Supplement 2). There were 14 patients (3%) who did not receive the methylprednisolone/placebo trial drug but received vasopressin/placebo and 8 patients (2%) who did not receive the vasopressin/placebo trial drug but received methylprednisolone/placebo (eTable 5 in Supplement 2). Of those receiving vasopressin/placebo, 139

Figure 1. Screening and Randomization in the VAM-IHCA Trial of Methylprednisolone and Vasopressin for In-Hospital Cardiac Arrest



[a] Logistic reasons included not enough personnel (n = 61), no study drug available (n = 45), inability to obtain surrogate consent (n = 1), and other (n = 32), which included patients isolated with COVID-19.

[b] Patients who were excluded after receiving the trial drugs had inclusion/exclusion criteria not known at the time of the cardiac arrest.

(28%), 145 (29%), 81 (16%), and 128 (26%) received 1, 2, 3, and 4 doses, respectively (eTable 5 in Supplement 2).

Primary Outcome

There were 100 patients (42%) in the intervention group and 86 patients (33%) in the placebo group who achieved return of spontaneous circulation, corresponding to a risk ratio of 1.30 (95% CI, 1.03-1.63; risk difference, 9.6% [95% CI, 1.1%-18.0%]; P = .03; **Table 2**). The risk ratio was slightly higher when adjusting for site and prognostic factors (risk ratio, 1.38 [95% CI, 1.10-1.72]). Results were generally consistent across predefined subgroups (**Figure 2**). The median time to return of spontaneous circulation was 16 minutes (first and third quartiles: 12, 25) in the intervention group and 18 minutes (first and third quartiles: 11, 31) in the placebo group.

Secondary Outcomes

At 30 days, 23 patients (9.7%) in the intervention group and 31 patients (12%) in the placebo group were alive (risk ratio, 0.83 [95% CI, 0.50-1.37]; risk difference, −2.0% [95% CI, −7.5% to 3.5%]; P = .48). A favorable neurologic outcome, based on the Cerebral Performance Category score, was observed in 18 patients (7.6%) in the intervention group and 20 patients (7.6%) in the placebo group at 30 days (risk ratio, 1.00 [95% CI, 0.55-1.83]; risk difference, 0.0% [95% CI, −4.7% to 4.9%]; P > .99). Results for survival and favorable neurologic outcome were generally consistent across predefined subgroups (eFigures 1 and 2 in Supplement 2).

Tertiary Outcomes

A favorable neurologic outcome at 30 days, based on the modified Rankin Scale score, was observed in 11 patients (4.6%) in the intervention group and 19 patients (7.2%) in the placebo group (risk ratio, 0.64 [95% CI, 0.32-1.31]; risk difference, −2.6% [95% CI, −6.9% to 1.7%]). Health-related quality of life did not differ between groups at 30 days (Table 2).

Outcomes at 90 days are presented in Table 2 and eFigure 3 in Supplement 2 and showed no statistically significant difference between groups.

Post-cardiac arrest organ dysfunction, as assessed by the SOFA score, were not statistically significantly different between groups, as were the number of vasopressor- and ventilator-free days (eTable 6 in Supplement 2). Additional details about the outcomes are reported in eTables 7, 8, and 9 in Supplement 2.

Adverse Events

Predefined potential adverse events are reported in eTable 10 in Supplement 2. In patients with return of spontaneous

Table 1. Baseline Characteristics According to Treatment Assignment[a]

Characteristic	No. (%)	
	Vasopressin and methylprednisolone (n = 237)	Placebo (n = 264)
Patient characteristics		
Age, y	71 (13)	70 (12)
Sex		
Male	148 (62)	174 (66)
Female	89 (38)	90 (34)
BMI[b]	26 (23-31)	26 (23-31)
Medical history[c]		
Arterial hypertension	148 (62)	167 (63)
Coronary artery disease	76 (32)	92 (35)
Atrial fibrillation	69 (29)	66 (25)
Diabetes	69 (29)	78 (30)
Pulmonary disease	67 (28)	82 (31)
Cancer	55 (23)	49 (19)
Kidney disease	54 (23)	49 (19)
Chronic heart failure	47 (20)	56 (21)
Stroke	46 (19)	40 (15)
Venous thromboembolism	15 (6)	14 (5)
Liver disease	8 (3)	11 (4)
Dementia	5 (2)	3 (1)
Any glucocorticoids prior to hospital admission	34 (14)	30 (11)
Interventions prior to cardiac arrest		
Kidney replacement therapy	25 (11)	20 (8)
Invasive mechanical ventilation	20 (8)	30 (11)
Vasopressor infusion	13 (5)	23 (9)
Cardiac arrest characteristics		
Location		
Hospital ward	163 (69)	168 (64)
Intensive care unit	23 (10)	18 (7)
Emergency department	19 (8)	38 (14)
Cardiac catherization laboratory	12 (5)	23 (9)
Operating room	4 (2)	3 (1)
Other[d]	16 (7)	14 (5)
Monitored	87 (37)	121 (46)
Witnessed	168 (71)	202 (77)
Initial rhythm		
Pulseless electrical activity	134 (57)	138 (52)
Asystole	82 (35)	95 (36)
Ventricular fibrillation	17 (7)	22 (8)
Ventricular tachycardia	4 (2)	9 (3)
Time from cardiac arrest recognition to		
Epinephrine administration, min	5 (3-7)	5 (3-8)
Drug administration, min	8 (6-12)	9 (6-12)

Abbreviation: BMI, body mass index.

[a] Continuous variables are presented as means with SDs or medians with first and third quartiles and categorical variables as counts and percentages.

[b] Data not available on 13 patients in the intervention group and 10 patients in the placebo group. Calculated as weight in kilograms divided by height in meters squared.

[c] Definitions are provided in eAppendix 2 in Supplement 2. Medical history was based on review of the electronical medical record.

[d] Other includes multiple different locations including the radiology department, the dialysis department, the psychiatric department, and outside departments (eg, hospital entrance).

circulation, hyperglycemia occurred in 77 (77%) in the intervention group and 63 (73%) in the placebo group. Hypernatremia occurred in 28 (28%) and 27 (31%) in the intervention and placebo groups, respectively.

Table 2. Outcomes According to Treatment Assignment[a]

	Vasopressin and methylprednisolone (n = 237)	Placebo (n = 264)	Difference, % (95% CI)[b]	Risk ratio (95% CI)	*P* value
Primary outcome					
Return of spontaneous circulation	100 (42)	86 (33)	9.6 (1.1 to 18.0)	1.30 (1.03 to 1.63)	.03
Secondary outcomes					
30-d Outcomes					
Survival	23 (9.7)	31 (12)	−2.0 (−7.5 to 3.5)	0.83 (0.50 to 1.37)	.48
Favorable neurologic outcome (CPC 1-2)[c]	18 (7.6)	20 (7.6)	0.0 (−4.7 to 4.9)	1.00 (0.55 to 1.83)	>.99
Favorable neurologic outcome (mRS 0-3)[d]	11 (4.6)	19 (7.2)	−2.6 (−6.9 to 1.7)	0.64 (0.32 to 1.31)	
EQ-5D-5L[e]	62 (15)	56 (23)	6 (−4 to 17)		
EQ-5D-5L-Index[e]	45 (37)	40 (33)	5 (−14 to 24)		
90-d Outcomes					
Survival	20 (8.4)	24 (9.1)	−0.7 (−5.7 to 4.5)	0.93 (0.53 to 1.62)	
Favorable neurologic outcome (CPC 1-2)[c]	18 (7.6)	20 (7.6)	0.0 (−4.7 to 4.9)	1.00 (0.55 to 1.83)	
Favorable neurologic outcome (mRS 0-3)[d]	15 (6.3)	20 (7.6)	−1.3 (−5.8 to 3.4)	0.84 (0.44 to 1.58)	
EQ-5D-5L[e]	70 (18)	69 (18)	1 (−9 to 11)		
EQ-5D-5L-index[e]	69 (32)	72 (26)	−3 (−20 to 14)		

Abbreviations: CPC, Cerebral Performance Category; EQ-5D-5L, EuroQol 5 Dimension 5 Level; mRS, modified Rankin Scale.

[a] Continuous variables are presented as means with SDs and categorical variables as counts and percentages.

[b] Risk difference for binary outcomes and mean difference for continuous outcomes.

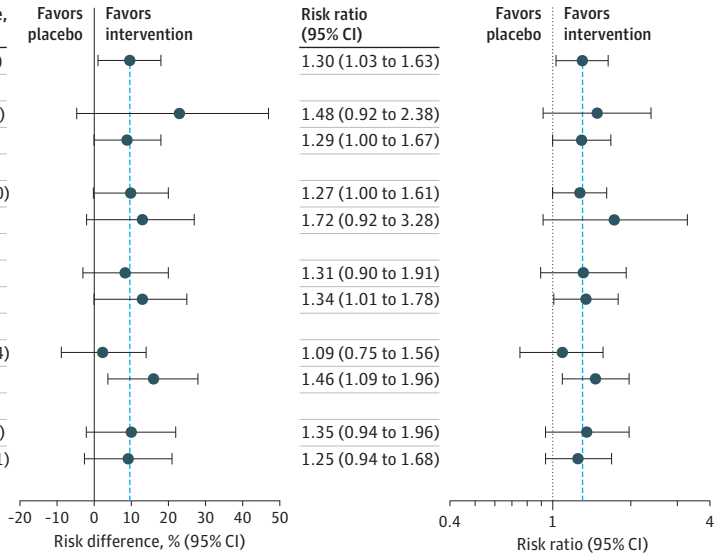
[c] Cerebral Performance Category is a 5-point scale assessing neurologic outcomes after brain damage, with higher scores indicating worse outcomes. A score of 1 or 2 is considered a favorable outcome.

[d] The mRS is a 7-point scale with higher scores indicating worse outcomes. A score of 0 to 3 is considered a favorable outcome.

[e] The results from the EQ-5D-5L are reported both as the numeric value directly assessed by the patient and as the indexed value. The numeric value is reported on a scale from 0 to 100, with higher scores indicating a better health-related quality of life, while the indexed value can also be negative.

Figure 2. Subgroups Results for Return of Spontaneous Circulation

	No./total (%)		Risk difference, % (95% CI)	Risk ratio (95% CI)
	Vasopressin and methylprednisolone	Placebo		
Overall	100/237 (42)	86/264 (33)	9.6 (1.1 to 18)	1.30 (1.03 to 1.63)
Initial rhythm				
Shockable	15/21 (71)	15/31 (48)	23 (-4.7 to 47)	1.48 (0.92 to 2.38)
Nonshockable	85/216 (39)	71/233 (30)	8.9 (0 to 18)	1.29 (1.00 to 1.67)
Witnessed				
Yes	79/168 (47)	75/202 (37)	9.9 (-0.2 to 20)	1.27 (1.00 to 1.61)
No	21/69 (30)	11/62 (18)	13 (-2 to 27)	1.72 (0.92 to 3.28)
Age, y				
>72	45/127 (35)	33/122 (27)	8.4 (-3 to 20)	1.31 (0.90 to 1.91)
≤72	55/110 (50)	53/142 (37)	13 (0.3 to 25)	1.34 (1.01 to 1.78)
Time from arrest to trial drug, min				
>8	38/115 (33)	41/135 (30)	2.7 (-8.8 to 14)	1.09 (0.75 to 1.56)
≤8	62/122 (51)	45/129 (35)	16 (3.7 to 28)	1.46 (1.09 to 1.96)
Time from epinephrine to trial drug, min				
>2	42/110 (38)	35/124 (28)	10 (-2.1 to 22)	1.35 (0.94 to 1.96)
≤2	58/127 (46)	51/140 (36)	9.2 (-2.6 to 21)	1.25 (0.94 to 1.68)



Subgroup results are presented for 5 predefined subgroups. Continuous variables were dichotomized at the median. The time of the cardiac arrest corresponds to the recognition of the cardiac arrest. The blue dashed lines indicate overall effect.

Discussion

In this trial, the combination of vasopressin and methylprednisolone compared with placebo administered during in-hospital cardiac arrest resulted in a statistically significant improvement in the primary outcome of return of spontaneous circulation. There were no differences in the secondary outcomes including survival and favorable neurologic outcome at 30 and 90 days.

The administration of vasopressin, which is also known as antidiuretic hormone, results in vasoconstriction. Because of this effect, vasopressin has been recommended as a second-line vasoactive agent in the setting of septic shock.[22] Vasoconstriction is also of interest in relation to cardiac arrest, because an increase in arterial blood pressure may increase the coronary perfusion pressure and thereby the chance of return of spontaneous circulation,[23,24] a prerequisite for longer-term survival. Despite these potential beneficial effects, trials of vasopressin in primarily out-of-hospital cardiac arrest have failed to show an improvement in outcomes, perhaps partly due to the late administration of drugs in this setting.[25] Corticosteroids, another drug often used in the setting of septic shock due to a reduction in vasopressor requirements,[26] exerts a wide range of functions in the body, including regulation of metabolism, inflammation, and cell proliferation. Studies in patients with cardiac arrest have demonstrated that levels of cortisol are higher in patients who have been resuscitated when compared with patients who have not been resuscitated,[27] which may illustrate an impaired endocrine response in nonsurvivors. This is supported by animal studies where the administration of hydrocortisone during cardiac arrest increased return of spontaneous circulation.[28] Data on glucocorticoid administration during human cardiac arrest are limited, and small studies have shown conflicting results.[29]

In the 2 trials by Mentzelopoulos et al,[6,7] the investigators found improvements in return of spontaneous circulation as well as an improvement in survival to hospital discharge. The current trial found an improvement in return of spontaneous circulation with a risk ratio of 1.30, which is consistent with the previous trials' findings.[6,7] However, contrary to the previous trials, there was no improvement in survival. In the current trial, the point estimate for survival suggested harm, while the confidence included both clinically relevant harm and benefit. There are a number of possible explanations for the difference in results between the current and the previous trials. First, the previous trials included the administration of post-cardiac arrest hydrocortisone to patients with circulatory shock in the intervention group.[6,7] Second, in the previous trials, research personnel administered the trial interventions, whereas it was administered by the clinical personnel in the current trial. Thus, while the current approach is more consistent with clinical practice, it might have resulted in a delay in the administration of the trial drugs compared with the previous trials. Third, there are important differences in patient characteristics. Patients in the previous trials were younger and more often had a cardiac arrest that was witnessed, occurring in the intensive care unit, and with an initial rhythm of asystole.[6,7] Survival in the control group was higher in the current trial despite a lower proportion of patients with return of spontaneous circulation.[6,7]

Trials within cardiac arrest have found that intracardiac arrest pharmacological interventions can increase return of spontaneous circulation with little or no clear improvement in long-term outcomes.[4,5] In the current trial, there was an absolute increase of 9.6% in return of spontaneous circulation. Other than epinephrine, this effect is larger than what previously has been shown for any other pharmacological intracardiac arrest intervention. Return of spontaneous circulation is the principal goal of cardiopulmonary resuscitation and a prerequisite for longer-term survival. The mechanistic goal of vasopressin and methylprednisolone is to increase return of spontaneous circulation and it is possible that other interventions, including post–cardiac arrest interventions, are needed to translate this effect into improvements in longer-term outcomes.

The current trial has strengths. Within the context of in-hospital cardiac arrest,[3] the trial was large and included more patients than the 2 previous trials combined. The trial was multicenter and included hospitals of various sizes. Long-term outcomes, including quality of life, were obtained from all patients with no loss to follow-up.

Limitations

The trial has several limitations. First, a large proportion of patients, who were potentially eligible, were not included (Figure 1). While this has no influence on the trial's internal validity, it could affect generalizability.

Second, while the median time to drug delivery was only 8 minutes, the drug was delivered relatively late in some patients. This could influence the results but is likely a reflection of clinical practice.

Third, the trial was powered to the primary outcome of return of spontaneous circulation. Given the much lower proportion of patients with survival and favorable neurologic outcome, the trial was not powered for these outcomes. The results cannot exclude potential benefit or harm of the intervention on these outcomes.

Fourth, while overall survival might appear low in the current trial (8%-9%), this is likely a reflection of the inclusion criteria, which required administration of at least 1 dose of epinephrine. Outcomes for cardiac arrest in Denmark are generally favorable compared with other countries.[2,3]

Conclusions

Among patients with in-hospital cardiac arrest, administration of vasopressin and methylprednisolone, compared with placebo, significantly increased the likelihood of return of spontaneous circulation. However, there is uncertainty whether this treatment results in benefit or harm for long-term survival.

ARTICLE INFORMATION

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Author Contributions: Dr Andersen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Andersen and Granfeldt.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Andersen and Granfeldt.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Andersen and Holmberg.
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