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Clinical paper

Vasopressin and methylprednisolone and hemodynamics after in-hospital cardiac arrest – A post hoc analysis of the VAM-IHCA trial

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Abstract

Introduction: The Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest (VAM-IHCA) trial demonstrated a significant improvement in return of spontaneous circulation (ROSC) with no clear effect on long-term outcomes. The objective of the current manuscript was to evaluate the hemodynamic effects of intra-cardiac arrest vasopressin and methylprednisolone during the first 24 hours after ROSC.

Methods: The VAM-IHCA trial randomized patients with in-hospital cardiac arrest to a combination of vasopressin and methylprednisolone or placebo during the cardiac arrest. This study is a post hoc analysis focused on the hemodynamic effects of the intervention after ROSC. Post-ROSC data on the administration of glucocorticoids, mean arterial blood pressure, heart rate, blood gases, vasopressor and inotropic therapy, and sedation were collected. Total vasopressor dose between the two groups was calculated based on noradrenaline-equivalent doses for adrenaline, phenylephrine, terlipressin, and vasopressin.

Results: The present study included all 186 patients who achieved ROSC in the VAM IHCA-trial of which 100 patients received vasopressin and methylprednisolone and 86 received placebo. The number of patients receiving glucocorticoids during the first 24 hours was 22/86 (26%) in the placebo group and 14/100 (14%) in the methylprednisolone group with no difference in the cumulative hydrocortisone-equivalent dose. There was no significant difference between the groups in the mean cumulative noradrenaline-equivalent dose (vasopressin and methylprednisolone: 603 ug/kg [95CI% 227; 979] vs. placebo: 651 ug/kg [95CI% 296; 1007], mean difference −48 ug/kg [95CI% −140; 42.9], $p = 0.30$), mean arterial blood pressure, or lactate levels. There was no difference between groups in arterial blood gas values and vital signs.

Conclusion: Treatment with vasopressin and methylprednisolone during cardiac arrest caused no difference in mean arterial blood pressure, vasopressor use, or arterial blood gases within the first 24 hours after ROSC when compared to placebo.

Keywords: In-hospital cardiac arrest, Vasopressin, Methylprednisolone, Hemodynamic

Introduction

In-hospital cardiac arrest occurs in approximately 2000 patients each year in Denmark and is a devastating condition with only approximately 30% of patients being alive after 30 days.[1,2] There are limited evidence-based treatments for patients with in-hospital cardiac arrest. In an effort to improve outcomes for patients with in-hospital cardiac arrest, the Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest (VAM-IHCA) trial was conducted.[3,4] The trial demonstrated a significant improvement in return of spontaneous circulation (ROSC) with vasopressin and methylprednisolone, but did not show an improvement long-term outcomes.[5] An individual participant data meta-analysis including the VAM-IHCA trial and two trials by Mentzelopoulos et al. also showed an improvement in return of spontaneous circulation, but more uncertain results for long-term outcomes, with wider 95% confidence intervals.[6–8]

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The rationale for administering vasopressin and glucocorticoids during in-hospital cardiac arrest is based on the profound vasoconstrictive effects of vasopressin and the hemodynamic and immunomodulatory effects of glucocorticoids.[9,10] While the combination of vasopressin and methylprednisolone has consistently been shown to improve ROSC,[8] the effects on hemodynamic function after ROSC are less clear.

The objective of the current manuscript was to evaluate the hemodynamic effects of intra-cardiac arrest vasopressin and methylprednisolone during the first 24 hours after ROSC.

Methods

Trial design

The trial protocol and primary and secondary results from the VAM-IHCA trial have previously been published.[3–5] The VAM-IHCA trial was an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group, double-blind trial of intra-cardiac arrest vasopressin and methylprednisolone during adult in-hospital cardiac arrest. The trial was approved by the regional ethics committee and the Danish Medicines Agency. Oral and subsequent written informed consent was temporarily obtained from a doctor independent of the trial until the patient regained consent capacity or a surrogate became available according to Danish legislation. Patients or surrogates provided consent for all patients that survived.

Patients

Patients were included from 10 hospitals in Denmark. Adult patients were eligible for the trial if they had an in-hospital cardiac arrest and received at least one dose of adrenaline during the cardiac arrest. Exclusion criteria included a clearly documented "do-not-resuscitate" order prior to the cardiac arrest, prior enrollment in the trial, invasive mechanical circulatory support at the time of the cardiac arrest, and known or suspected pregnancy at the time of the cardiac arrest. The present study included patients who achieved ROSC, which was defined as spontaneous circulation with no further need for chest compressions sustained for at least 20 minutes.[4]

Intervention

The trial drugs consisted of 40 mg methylprednisolone (Solu-Medrol®, Pfizer) and 20 IU of vasopressin (Empressin®, Amomed Pharma GmbH) given as soon as possible after the first dose of adrenaline. Additional doses of vasopressin (20 IU) were administered after each adrenaline dose for a maximum of four doses (80 IU). The trial was double-blind with patients, investigators, clinicians, and outcome assessors being unaware of the allocated treatment.

Outcomes

The primary and secondary outcomes of the trial have been reported previously.[4,5] This manuscript is a post hoc analysis focusing on the hemodynamic effects of vasopressin and methylprednisolone compared to placebo in the first 24 hours after ROSC. We collected data on the administration of glucocorticoids, vital signs, arterial blood gases, vasopressor and inotropic therapy, and sedation.

Our primary interest was in the hemodynamic effects of the interventions compared to placebo after ROSC. Doses and infusion rates of the following vasopressors and inotropes were collected hourly for the first 24 hours after ROSC: noradrenaline, adrenaline, dobutamine, milrinone, levosimendan, terlipressin, phenylephrine, vasopressin, and dopamine. To be able to compare total vasopressor dose between the two groups, we calculated noradrenaline-equivalent doses for adrenaline, phenylephrine, terlipressin, and vasopressin based on Kotani et al. (Table S1).[11]

We collected data on the use of glucocorticoids after ROSC and calculated hydrocortisone-equivalent doses (Table S2).[12] Blood pressure, heart rate, doses, and infusion rates of sedative agents were collected hourly. Arterial blood gases were collected hourly if data was available.

Statistical analysis

The analyses only included patients receiving at least the first dose of either of the trial drugs, meeting all inclusion criteria and no exclusion criteria, and achieving ROSC. Patients were analyzed according to their randomized assignment.

Continuous data are presented as medians with first and third quartiles. Binary data are presented as counts and percentages.

To compare hourly repeated values (blood pressures, heart rates, arterial blood gas values, and noradrenaline-equivalent doses) between groups, we used a linear mixed model with a random intercept for each patient. The models included fixed effects for group, time, and interactions between group and time. Time from ROSC to 24 hours after was modelled as a continuous variable with linear and quadratic terms. Models were also adjusted for site, age (linear continuous variable), witnessed status, and initial rhythm (shockable and non-shockable).[13] Using these models, we did an overall comparison between the groups using likelihood ratio tests and present the results graphically. In addition, using the model, we compared values at 2, 6, 12, and 24 hours between the two groups.

We compared the cumulative noradrenaline-equivalent dose at 2, 6, 12, and 24 hours using generalized linear models (normal distribution and identity link function) with robust standard errors with adjustment for the same variables as above. Similar analyses were performed for cumulative hydrocortisone-equivalent doses at 24 hours.

For the primary analyses, patients who died within 24 hours were assigned missing values from death until 24 hours. For the cumulative noradrenaline-equivalent dose at 2, 6, 12, and 24 hours, we conducted two sensitivity analyses. In the first, we only included patients that survived the first 24 hours. In the second, the last recorded value for those dying was extrapolated until 24 hours.

Additional data are presented descriptively.

Results

Patient characteristics and early outcomes

In the original VAM-IHCA trial, 501 patients were randomized, received the trial drugs, and were included in the analyses. Of these, 186 achieved ROSC and were included in the present study with 100 patients in the vasopressin and methylprednisolone group and 86 in the placebo group (Fig. 1). Baseline characteristics were overall comparable between the groups, although there was a higher proportion of witnessed and monitored cardiac arrest in the placebo group (Table 1).

The number of patients receiving glucocorticoids during the first 24 hours was 22/86 (26%) in the placebo group and 14/100 (14%) in the methylprednisolone group (Table 2). There was no statistically significant difference in the mean cumulative hydrocortisone-

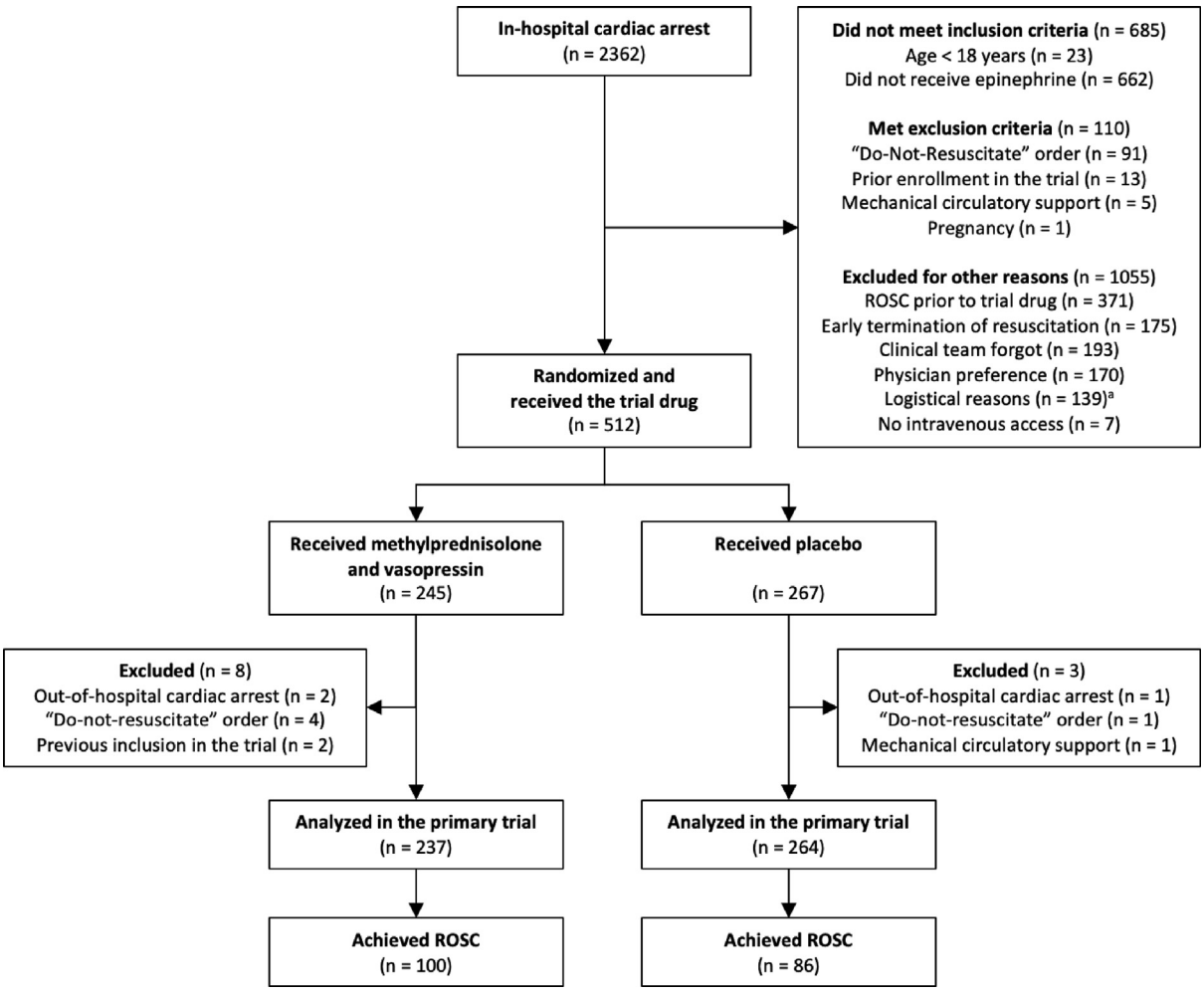

Fig. 1 – Inclusion and exclusion criteria. [a] Logistic reasons include inability to obtain surrogate consent (n = 1), no trial drug available (n = 45), not enough personnel (n = 61), and other (n = 32) which included patients isolated with COVID-19.

equivalent dose (vasopressin and methylprednisolone: 250 ug/kg [95CI% 15; 485] vs. placebo: 274 ug/kg [95CI% 45; 503], mean difference −24 ug/kg [95CI% −98; 50], p = 0.53) (Table S3). More patients in the placebo group were on extracorporeal cardiopulmonary resuscitation and more received coronary angiography and percutaneous coronary intervention in the first 24 hours. In the vasopressin and methylprednisolone group, 62/100 (62%) were alive at 24 hours with 59/86 (69%) alive in the placebo group (Fig. 2).

Hemodynamic function

Noradrenaline was the most commonly used vasopressor with 71/100 (71%) receiving any dose during the first 24 hours in the vasopressin and methylprednisolone group and 69/86 (80%) in the placebo group (Table S4). Only 4 patients in the placebo group received vasopressin after ROSC with no patients in the intervention group receiving vasopressin after ROSC. The most commonly used inotropic agents were dobutamine and milrinone but these were rarely used (≤15%, Table S4).

The noradrenaline-equivalent dose of vasopressors over the first 24 hours is presented in Fig. 3. There was no statistically significant difference between the groups in hourly noradrenaline-equivalent dose or mean cumulative noradrenaline-equivalent dose (vasopressin and methylprednisolone: 603 ug/kg [95CI% 227; 979] vs. placebo: 651 ug/kg [95CI% 296; 1007], mean difference: −48 ug/kg [95CI% −140; 43], p = 0.30, Table S3). The two sensitivity analyses including only patients surviving 24 hours and with the last observation carried forward yielded similar results with no statistically significant differences between groups (Table S5).

Heart rate and mean arterial blood pressure were comparable between groups (Fig. 4, Fig. S1, and Table S6). Lactate levels were elevated following ROSC with a normalization during the first 12 hours in both groups. There was a statistically significant increase in lactate at 24 hours in the vasopressin and methylprednisolone group compared to the placebo group (Fig. 4 and Table S6).

Laboratory values

Laboratory values are presented in Table S6 and Fig. S2-3. Overall, no significant differences existed between the groups. Glucose levels decreased during the first 24 hours with no difference between groups. No difference in sodium levels was observed for the first 12 hours, but with higher levels in the vasopressin and methylprednisolone group at 24 hours (Table S6).

Table 1 – Baseline characteristics according to assigned treatment.

	Overall (*n* = 186)	Vasopressin and Methylprednisolone (*n* = 100)	Placebo (*n* = 86)
Patient Characteristics			
Age – years	71 (59, 77)	71 (63, 78)	71 (57, 77)
Male sex – no. (%)	118 (63)	65 (65)	53 (62)
Past medical history – no. (%)			
Coronary artery disease	57 (31)	31 (31)	26 (30)
Chronic heart failure	28 (15)	15 (15)	13 (15)
Atrial fibrillation	45 (24)	25 (25)	20 (23)
Stroke	22 (12)	16 (6)	6 (7)
Venous thromboembolism	11 (6)	8 (8)	3 (3)
Hypertension	112 (60)	62 (62)	50 (58)
Diabetes	50 (27)	30 (30)	20 (23)
Pulmonary disease	59 (32)	29 (29)	30 (35)
Renal disease	32 (17)	22 (22)	10 (12)
Liver disease	7 (4)	4 (4)	3 (3)
Cancer	33 (24)	27 (27)	17 (20)
Dementia	0 (0)	0 (0)	0 (0)
Cardiac Arrest Characteristics			
Location – no. (%)			
Emergency department	19 (10)	7 (7)	12 (14)
Hospital ward	110 (59)	61 (61)	49 (57)
Intensive care unit	21 (11)	15 (15)	6 (7)
Operating room	2 (1)	1 (1)	1 (1)
Cardiac catheterization laboratory	16 (9)	5 (5)	11 (13)
Other	18 (10)	11 (11)	7 (8)
Monitored – no. (%)	81 (44)	37 (37)	44 (51)
Witnessed – no. (%)	154 (83)	79 (79)	75 (87)
Initial rhythm – no. (%)			
Asystole	53 (28)	31 (31)	22 (26)
Pulseless electrical activity	103 (55)	54 (54)	49 (57)
Ventricular fibrillation	24 (13)	12 (12)	12 (14)
Ventricular tachycardia	6 (3)	3 (3)	3 (3)
Time to adrenaline administration – minutes	5 (3, 7)	4 (3, 7)	5 (3, 8)
Time to trial drug administration – minutes	8 (6, 11)	8 (6, 10)	8 (6, 12)

Continuous variables are presented as medians with first and third quartiles and categorical variables as numbers and percentages.

Table 2 – Interventions after return of spontaneous circulation.

	Overall (*n* = 186)	Vasopressin and Methylprednisolone (*n* = 100)	Placebo (*n* = 86)
Glucocorticoid administration[a]	36 (19)	14 (14)	22 (26)
Type of glucocorticoids			
Hydrocortisone	24 (13)	7 (50)	17 (77)
Dexamethasone	2 (1)	1 (7)	1 (5)
Methylprednisolone	4 (2)	3 (21)	1 (5)
Fludrocortisone	0 (0)	0 (0)	0 (0)
Prednisone	1 (1)	1 (7)	0 (0)
Prednisolone	5 (3)	2 (14)	3 (14)
Total dose of glucocorticoids (mg)[b]	100 (16, 200)	50 (9, 150)	100 (100, 200)
ECPR anytime	25 (13)	8 (8)	17 (20)
Coronary angiography	38 (20)	15 (15)	23 (27)
Percutaneous coronary intervention	23 (12)	8 (8)	15 (17)
Echocardiography	147 (79)	73 (73)	74 (86)
Ejection fraction (%)[c]	25 (15, 40)	25 (18, 43)	30 (10, 40)
24-hour survival	121 (65)	62 (62)	59 (69)

Abbreviations: ECPR, extracorporeal cardiopulmonary resuscitation.

Categorical variables are presented as numbers and percentages.

[a] Any administration during the first 24 hours after return of spontaneous circulation.

[b] Hydrocortisone-equivalent dose.

[c] Ejection fraction missing in 68 (68%) patients receiving vasopressin and methylprednisolone and in 51 (59%) patients receiving placebo.

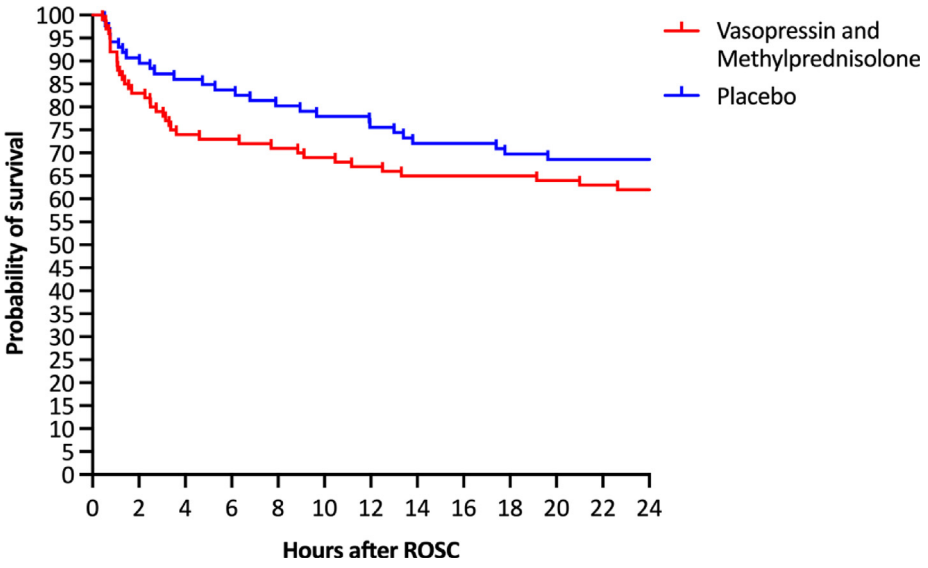

Fig. 2 – 24- hour survival curve for patients achieving return of spontaneous circulation. Of the 100 subjects assigned to the vasopressin and methylprednisolone group, 62 (62%) were alive at 24 hours. Of the 86 subjects assigned to the placebo group, 59 (69%) were alive at 24 hours.

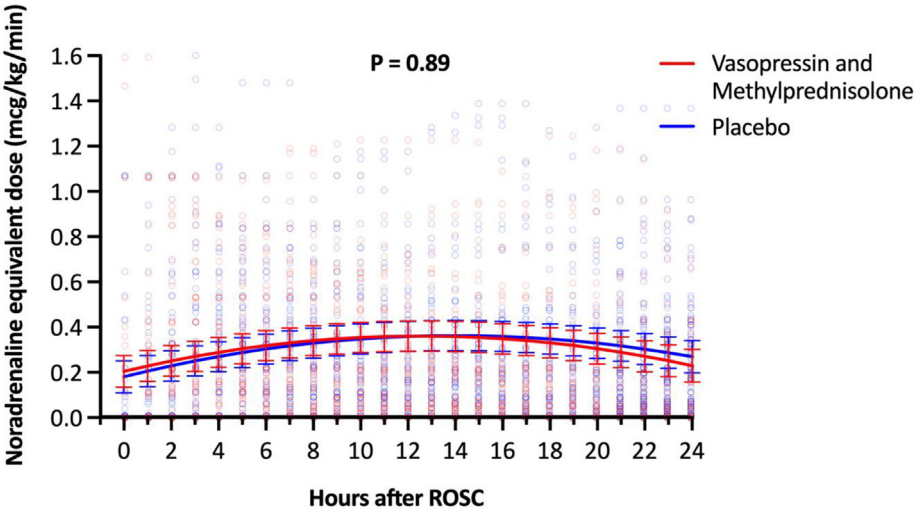

Fig. 3 – Noradrenaline equivalent dose. The lines represent the estimated total noradrenaline-equvalent dose with 95% confidence intervals at each hour after return of spontaneous circulation. The circles represent the total noradrenaline-equvalent dose for individual patients.

Sedation

Propofol was the most commonly used sedative agent with 46/100 (46%) receiving propofol in the vasopressin and methylprednisolone group and 48/86 (56%) in the placebo group (Table S7 and Fig. S4). The most commonly used opioids were remifentanil and fentanyl.

Discussion

The current post hoc analysis of a randomized clinical trial investigated the effects of vasopressin and methylprednisolone on hemodynamic function, vasopressor use, and arterial blood gases during the first 24 hours after ROSC. The results showed that vasopressin and methylprednisolone administered during cardiac arrest caused no difference in blood pressure, vasopressor use, or arterial blood gas values during the first 24 hours after ROSC when compared to placebo.

The VAM-IHCA trial was based on the promising findings by Mentzelopoulos et al. showing an improvement in ROSC and long-term outcomes with vasopressin and methylprednisolone.[6,7] Our findings, i.e., no effect on post-resuscitation hemodynamic function and vasopressor use, are in contrast to those previous trials. Mentzelopoulos et al. reported significantly lower post-resuscitation vasopressor usage, lower levels of IL-6, and higher mean arterial

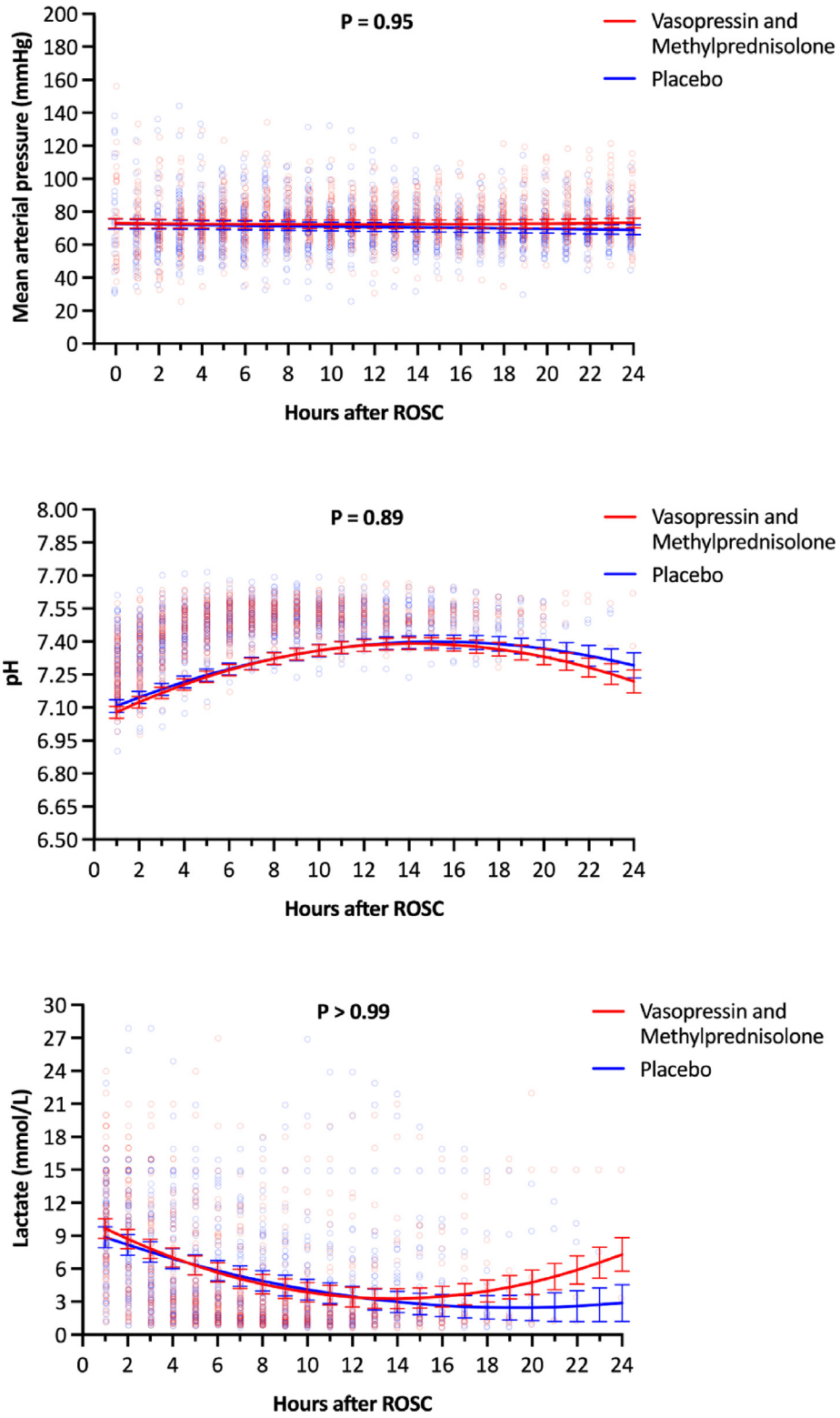

Fig. 4 – Mean arterial pressure, pH, and lactate. The lines represent the estimated mean arterial blood pressure, pH, and lactate values with 95% confidence intervals at each hour after return of spontaneous circulation. The circles represent the raw values for each patient.

pressures in the intervention groups.[6,7] This difference in findings could partially relate to the treatment protocol in the trials by Mentzelopoulos et al., which included a daily dose of 300 mg hydrocortisone in patients with post-resuscitation shock at 4 hours.[6,7] Hydrocortisone in these doses is known for its vasopressor-sparing effects in patients with sepsis and its profound immunomodulatory effects.[14,15]

However, in post-cardiac arrest patients, a small randomized trial of 50 patients demonstrated no effect on time to shock reversal with the administration of hydrocortisone.[16] Post-resuscitation hydrocortisone was not included in the VAM-IHCA trial for pragmatic reasons and to specifically test only the intra-cardiac arrest intervention.

The combination of vasopressin and methylprednisolone significantly increased the number of patients achieving ROSC in the VAM-IHCA trial (42% vs. 33%, risk difference 9.6% [95%CI 1.1–18.0%]). The 24-hour survival curve presented in this study demonstrates that a high number of patients in the intervention group died within the first hours after ROSC. When administered intravenously, vasopressin has a half-life of approximately 10–35 minutes. Methylprednisolone on the other hand has a biological half-life of approximately 12–36 hours. As such, any effect of the intra-cardiac arrest methylprednisole dose could potentially be observed during the first 24 hours.[10,17–19] The half-life for the non-genomic cardiovascular effects of methylprednisolone is unknown.[20,21]

The administration of vasopressin and methylprednisolone may provide immediate beneficial cardiovascular effects during resuscitation resulting in ROSC in patients that would not otherwise have been resuscitated. A similar observation has been proposed for adrenaline. In the PARAMEDIC2 trial, adrenaline administered during cardiac arrest resulted in an approximate 300% relative increase in ROSC, with only a relatively small effect (approximately 30% relative increase) on long-term survival.[22] Although ROSC is a prerequisite for survival, larger trials are needed to determine whether there is an effect of vasopressin and methylprednisolone on longer-term outcomes. Ongoing trials are currently investigating the effect of vasopressin and methylpredisolon for in-hospital cardiac arrest (clinialtrial.gov NCT05139849) and the effect of methylprednisolone for out-of-hospital cardiac arrest.[23]

This study has a number of important limitations. It was a post-hoc exploratory analysis with post-hoc data collection. However, data collection was performed blinded and the statistical analysis was pre-planned prior to data analysis limiting potential bias. Although the study was a randomized controlled trial, it is important to consider that the groups included in this study (i.e., those with ROSC) are not balanced as the intervention increased the rate of ROSC. This increased the number of patients admitted to the ICU in the intervention group. This imbalance is evidenced by a lower prevalence of witnessed and monitored cardiac arrests in the intervention group, which could illustrate a more severe phenotype. This is consistent with the hypothesis that the intervention resulted in ROSC in patients who would not otherwise have had ROSC. Furthermore, although the trial was double-blind, the intervention could make patients present different clinically due to effects of the interventions, affecting post-resuscation interventions such as use of steroids, coronary angiography, and percutaneous coronary intervention. This makes a direct comparison between the groups difficult. The study is limited by a lack of data during cardiac arrest and in the immediate post-resuscitation period. The majority of cardiac arrests occured in locations where patients are not invasively monitored prior to the cardiac arrest, hence, in most cases the first data is collected after admission to the ICU. As post-resuscation care was not protocolized, the choice of hemodynamic targets and vasopressor use were at the discretion of the treating physician. We tried to adjust for this potential limitation by using noradrenaline- and hydrocorticonse-equvalent doses as previously described.[11,12]

Conclusion

Treatment with vasopressin and methylprednisolone during cardiac arrest caused no difference in mean arterial blood pressure, vasopressor use, or arterial blood gases within the first 24 hours after ROSC when compared to placebo.

Funding/support

Funding for the trial was provided by Aarhus University Research Foundation; the Department of Clinical Medicine, Aarhus University; the Central Denmark Region; and the Independent Research Fund Denmark. Empressin and corresponding placebo ampoules were provided free of charge by Amomed Pharma GmbH.

Role of the Funder/Sponsor

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

CRediT authorship contribution statement

Lars W. Andersen: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Mathias J. Holmberg:** Writing – review & editing, Validation, Methodology, Formal analysis, Data curation. **Maria Høybye:** Writing – review & editing, Validation, Project administration, Data curation. **Dan Isbye:** Writing – review & editing, Project administration, Investigation, Data curation. **Jesper Kjærgaard:** Writing – review & editing, Project administration, Investigation, Data curation. **Søren Darling:** Writing – review & editing, Project administration, Investigation, Data curation. **Stine T. Zwisler:** Writing – review & editing, Project administration, Investigation, Data curation. **Jacob M. Larsen:** Writing – review & editing, Project administration, Investigation, Data curation. **Bodil S. Rasmussen:** Writing – review & editing, Project administration, Investigation, Data curation. **Kasper Iversen:** Writing – review & editing, Project administration, Investigation, Data curation. **Martin Schultz:** Writing – review & editing, Project administration, Investigation, Data curation. **Birthe Sindberg:** Writing – review & editing, Project administration, Investigation, Data curation. **Mikael Fink Valentin:** Software, Validation, Writing – review & editing. **Asger Granfeldt:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AG: DSMB member Noorik Biopharmaceuticals and consultant NMD pharma, outside the submitted work. JK: Grant from the Novo

Nordisk Foundation (NNF17OC0028706 and NNF22OC0079649) outside the current work. The remaining authors report no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.resuscitation.2023.109922.

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