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Short paper

Effect of vasopressin and methylprednisolone vs. placebo on long-term outcomes in patients with in-hospital cardiac arrest a randomized clinical trial

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Abstract

Objective: The primary results from the Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest (VAM-IHCA) trial have previously been reported. The objective of the current manuscript is to report long-term outcomes.

Methods: The VAM-IHCA trial was a multicenter, randomized, double-blind, placebo-controlled trial conducted at ten hospitals in Denmark. Adult patients (age $\geq$ 18 years) were eligible for the trial if they had an in-hospital cardiac arrest and received at least one dose of epinephrine during resuscitation. 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 epinephrine. This manuscript report outcomes at 6 months and 1 year including survival, survival with favorable neurological outcome, and health-related quality of life.

Results: 501 patients were included in the analysis. At 1 year, 15 patients (6.3%) in the intervention group and 22 patients (8.3%) in the placebo group were alive corresponding to a risk ratio of 0.76 (95% CI, 0.41–1.41). A favorable neurologic outcome at 1 year, based on the Cerebral Performance Category score, was observed in 14 patients (5.9%) in the intervention group and 20 patients (7.6%) in the placebo group (risk ratio, 0.78 [95% CI, 0.41–1.49]. No differences existed between groups for favorable neurological outcome and health-related quality of life at either 6 months or 1 year.

Conclusions: Administration of vasopressin and methylprednisolone, compared with placebo, in patients with in-hospital cardiac arrest did not improve long-term outcomes in this trial.

Keywords: In-hospital cardiac arrest, Vasopressin, Methylprednisolone, Long-term, Outcomes

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Introduction

Despite in-hospital cardiac arrest being a frequent event with a high mortality, the number of trials focused on improving outcomes for this patient population is scarce.[1]

In 2009 and 2013, Mentzelopoulos et al. published two randomized, double-blind trials, comparing the addition of vasopressin and one dose of glucocorticoids during in-hospital cardiac arrest to placebo.[2,3] The trials showed a large improvement in return of spontaneous circulation and survival to hospital discharge. To confirm these promising findings, the Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest (VAM-IHCA) trial was conducted.[4,5] The primary short-term outcomes were recently published demonstrating a significant increase in return of spontaneous circulation with the intervention with no difference in survival or survival with a favorable outcome at 30 and 90 days.[5] A recent systematic review and meta-analysis of individual participant data also demonstrated an increase in return of spontaneous circulation while the results for survival or survival with a favorable outcome were more uncertain.[6]

The objective of the current manuscript was to report long-term outcomes and to describe the change in outcomes and treatment effect over time.

Methods

Trial design and oversight

The trial protocol and primary results have previously been published.[4,5] The VAM-IHCA 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. 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 (age $\geq$ 18 years) were eligible for the trial if they had an in-hospital cardiac arrest and received at least one dose of epinephrine 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 (extracorporeal circulation or left ventricular assist devise) at the time of the cardiac arrest, and known or suspected pregnancy at the time of the cardiac arrest.

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 epinephrine. Additional doses of vasopressin (20 IU) were administered after each epinephrine 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

This manuscript focuses on 6-month and 1-year outcomes including survival, survival with favorable neurological outcome, and health-related quality of life assessed using the EQ-5D-5L.[7,8] A favorable neurologic outcome was defined as a Cerebral Performance Category score of 1 or 2. Neurologic outcome was also assessed using the modified Rankin Scale.[9] A score of 0 to 3 was considered a favorable outcome. The results from the EQ-5D-5L are reported both as the numeric value directly assessed by the patient and as the indexed value.[7,10] 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 primarily by telephone interview. If the patient was not able to participate, a relative or clinical personnel provided the assessment.

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.[5]

Binary data are presented as counts with percentages and continuous data are presented as means with standard deviations (SD). Differences between groups are presented as both risk differences and risk ratios with 95% confidence intervals.[11] Differences between groups in continuous outcomes are presented as mean differences with 95% confidence intervals obtained from generalized linear models with robust errors. Subgroup analyses 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. While the subgroups were pre-defined, the subgroup analyses for the long-term outcomes were not.

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

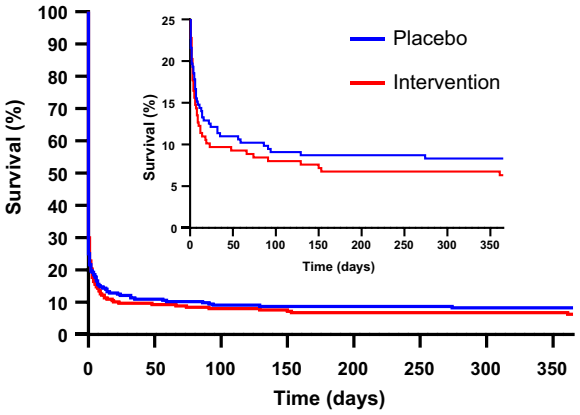

Fig. 1 – Survival over time. Large figure: Plot of Survival over time with survival on the y-axis and time in days on the x-axis. Small figure: Y-axis stopping at 25% as a large number of patients never achieve return of spontaneous circulation and die at day 0.

Results

Patient characteristics

501 patients were included in the analysis, with 237 in the intervention group and 264 in the placebo group. There was no loss to follow-up. Detailed patient characteristics have been reported elsewhere.[5] Baseline characteristics were balanced between the two groups. The mean (SD) age was 71 (13) years and 322 (64%) were men. Most cardiac arrest occurred in the ward (66%), were witnessed (74%), and presented with an initial nonshockable rhythm (90%).

Outcomes

Survival over time is displayed in Fig. 1. Outcomes at 6 months and 1 year are presented in Table 1 along with already reported outcomes at 30 and 90 days for comparison. At 6 months, there were 16 patients (6.8%) in the intervention group and 23 patients (8.7%) in the placebo group who were alive corresponding to a risk ratio of 0.77 (95% CI, 0.42–1.42; risk difference, −2.0% [95% CI, −6.8%–2.9%], Table 1). At 1 year there were 15 patients (6.3%) in the intervention group and 22 patients (8.3%) in the placebo group who were alive corresponding to a risk ratio of 0.76 (95% CI, 0.41–1.41; risk difference, −2.0% [95% CI, −6.7%–2.7%], Table 1). No differences existed between groups for favorable neurological outcome and health-related quality of life at either 6 months or 1 year (Table 1).

Results for survival at 1 year were generally consistent across the five predefined subgroups with no effect of the intervention, except for a signal in favor of placebo with longer time to administration (Fig. 2).

Discussion

This manuscript report on long-term outcomes following randomization to either vasopressin and methylprednisolone or placebo during in-hospital cardiac arrest. No effect of the intervention was observed at 6 months or 1 year, although the confidence intervals were wide and the results do not exclude potential benefit or harm. The results are in line with the primary findings of a significant effect on return of spontaneous circulation but no effect on survival or survival with a favorable neurological outcome at 30 and 90 days.[5] The current manuscript is the first to report on long-term outcomes following administration of vasopressin and methylprednisolone. The previous trials included follow-up to 60 days after randomization.[2,3] The subgroup analysis potentially showing that a longer time to trial drug administration favors the placebo group is in line with our previous systematic review where the potential beneficial effect of the intervention at hospital discharge diminished with increasing time to drug administration.[6] This highlights the importance of early administration in order to detect a potential beneficial effect in future trials.

Table 1 – Outcomes according to treatment assignment.

	Vasopressin and Methylprednisolone (*n* = 237)	Placebo (*n* = 264)	Risk ratio (95%CI)	Difference[a] (95%CI)
30-Day outcomes				
Survival	23 (9.7%)	31 (12%)	0.83 (0.50, 1.37)	−2.0% (−7.5, 3.5)
Favorable neurologic outcome (CPC 1–2)	18 (7.6%)	20 (7.6%)	1.00 (0.55, 1.83)	0.0% (−4.7, 4.9)
Favorable neurologic outcome (mRS 0–3)	11 (4.6%)	19 (7.2%)	0.64 (0.32, 1.31)	−2.6% (−6.9, 1.7)
EQ-5D-5L	62 (15)	56 (23)	–	6 (−4, 17)
EQ-5D-5L – Index	45 (37)	40 (33)	–	5 (−14, 24)
90-Day outcomes				
Survival	20 (8.4%)	24 (9.1%)	0.93 (0.53, 1.62)	−0.7% (−5.7, 4.5)
Favorable neurologic outcome (CPC 1–2)	18 (7.6%)	20 (7.6%)	1.00 (0.55, 1.83)	0.0% (−4.7, 4.9)
Favorable neurologic outcome (mRS 0–3)	15 (6.3%)	20 (7.6%)	0.84 (0.44, 1.58)	−1.3% (−5.8, 3.4)
EQ-5D-5L	70 (18)	69 (18)	–	1 (−9, 11)
EQ-5D-5L – Index	69 (32)	72 (26)	–	−3 (−20, 14)
6-Month outcomes				
Survival	16 (6.8%)	23 (8.7%)	0.77 (0.42, 1.42)	− 2.0% (−6.8, 2.9)
Favorable neurologic outcome (CPC 1–2)	15 (6.3%)	20 (7.6%)	0.84 (0.44, 1.58)	− 1.3% (−5.8, 3.4)
Favorable neurologic outcome (mRS 0–3)	14 (5.9%)	20 (7.6%)	0.78 (0.41, 1.49)	− 1.7% (−6.2, 2.9)
EQ-5D-5L	76 (15)	75 (14)	–	1 (−8, 10)
EQ-5D-5L – Index	82 (24)	76 (25)	–	6 (−9, 21)
1-Year outcomes				
Survival	15 (6.3%)	22 (8.3%)	0.76 (0.41, 1.41)	−2.0% (−6.7, 2.7)
Favorable neurologic outcome (CPC 1–2)	14 (5.9%)	20 (7.6%)	0.78 (0.41, 1.49)	−1.7% (−6.2, 2.9)
Favorable neurologic outcome (mRS 0–3)	12 (5.1%)	20 (7.6%)	0.67 (0.34, 1.32)	−2.5% (−7.0, 1.9)
EQ-5D-5L	76 (14)	79 (14)	–	−2 (−12, 7)
EQ-5D-5L – Index	83 (19)	81 (21)	–	2 (−11, 15)

Continuous variables are presented as means with standard deviations and categorical variables as counts and percentages. CPC refers to Cerebral Performance Status which 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. mRS refers to modified Rankin Scale, which is a 7-point scale with higher scores indicating worse outcomes. A score of 0 to 3 is considered a favorable outcome. 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.

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

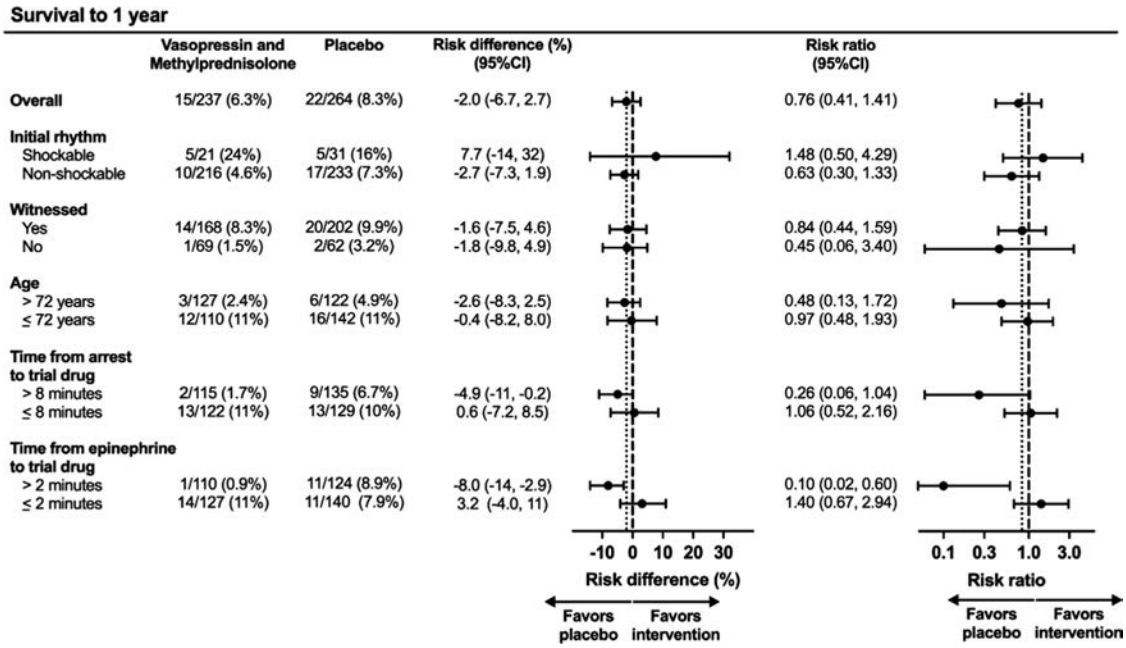

Fig. 2 – Subgroups results for 1 year survival. Subgroup results are presented for five pre-defined subgroups. Continuous variables were dichotomized at the median. The time of the cardiac arrest correspond to the recognition of the cardiac arrest.

The optimal time point for outcome reporting in cardiac arrest studies is unknown.[12] Short-term outcomes, such as survival to hospital discharge or 30-day survival, are often reported, while collection of long-term outcomes requires more resources and often result in a higher loss to follow-up. Although neurological recovery may improve over time, studies have demonstrated a decrease in survival over time exceeding that of non-cardiac arrest hospital controls and the background population.[13,14] This is consistent with our findings of a decrease in survival during the 1-year follow-up period. However, when evaluating the effect of an intervention, the aim is to evaluate whether the treatment effect changes over time and not just survival. This is especially important in patients with cardiac arrest due to a high comorbidity burden such that patients may die from their underlying disease during the follow-up period unrelated to the cardiac arrest and/or intervention. In the current trial, the treatment effect remained relatively unchanged over time although a formal assessment of this was limited by the low event rate. An unchanged long-term treatment effect was also observed in the PARAMEDIC2 (Prehospital Assessment of the Role of Adrenaline: Measuring the Effectiveness of Drug Administration in Cardiac Arrest) trial.[15,16] This might indicate that long-term outcomes may not always provide additional information when evaluating treatment effects as it may depend on the type of intervention. Interventions such as adrenaline and vasopressin and methylprednisolone, both with the primary aim of increasing return of spontaneous circulation, may have unchanged effect estimates over time, whereas interventions targeting neurological injury potentially could change effect estimates over time.

Limitations

The number of patients with long-term survival was low resulting in wide confidence intervals.

Conclusion

Administration of vasopressin and methylprednisolone, compared with placebo, in patients with in-hospital cardiac arrest did not improve long-term outcomes in this trial.

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.

Conflict of Interest

Dr Andersen reported receiving grants from Aarhus University Research Foundation, the Department of Clinical Medicine at Aarhus University, and Independent Research Fund Denmark, and nonfinancial support from Amomed Pharma GmbH, which provided trial drug during the conduct of the study. Dr J. Kjærgaard reported receiving grants from the Novo Nordisk Foundation (NNF17OC0028706) outside the submitted work. Dr Lauridsen reported receiving grants from Independent Research Fund Denmark during the conduct of the study. Dr Granfeldt reported receiving personal fees from Noorik Biopharmaceuticals outside the submitted work. No other disclosures were reported.

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