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EFFICACY OF VASOPRESSIN-METHYLPREDNISOLONE VS PLACEBO FOR IN-HOSPITAL CARDIAC ARREST: SYSTEMATIC REVIEW

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ABSTRACT
Intrahospital cardiac arrest (IHCA) has a high mortality (70-90%) despite standard resuscitation. The combination of vasopressin and methylprednisolone has been proposed as an adjuvant therapy to improve Return of Spontaneous Circulation (ROSC) and patient outcomes, but evidence of its effectiveness on long-term survival remains controversial. Objective to evaluate the efficacy of vasopressin-methylprednisolone combination versus placebo in IHCA patients for ROSC, survival, and neurologic outcomes. This systematic review study used the PICO framework (Population: Cardiac Arrest In-Hospital Patients; Intervention: Vasopressin + Methylprednisolone; Comparison: Placebo; Outcome: ROSC) and Randomized Controlled Trials (RCT) study design. A search in PubMed, ScienceDirect, and Google Scholar using the keywords "Vasopressin, Cardiac Arrest In-Hospital, Methylprednisolone, ROSC" resulted in a total of 769,070 initial articles. After screening based on access criteria, language, design, and publication year (2020-2025), 196 articles remained. Further eligibility selection based on sample suitability and specific interventions resulted in 41 potential articles. The final analysis to answer the question of the effect of the combination of Vasopressin and Methylprednisolone on ROSC found 3 RCT journals (from PubMed) that met all inclusion criteria. The combination of vasopressin-methylprednisolone significantly increased ROSC (42% vs. 33%; RR 1.30; 95% CI 1.03–1.63; *p* = 0.03), especially when given ≤8 minutes after cardiac arrest (51% vs. 35%). However, there were no significant differences in 30-day (9.7% vs. 12%; RR 0.83) or 1-year survival (6.3% vs. 8.3%; RR 0.76), favorable neurologic outcome (Cerebral Performance Category 1–2: 7.6% vs. 7.6%), or quality of life (EQ-5D-5L score). Adverse events (hyperglycemia, hypernatremia) were similar between groups. The combination of vasopressin-methylprednisolone effectively improves ROSC but has no impact on long-term survival or neurological recovery. Further studies are needed to identify subpopulations that benefit and explore post-ROSC therapeutic strategies.

Keywords: in-hospital cardiac arrest; methylprednisolone; ROSC; vasopressin

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INTRODUCTION

Intrahospital cardiac arrest (IHCA) is a life-threatening emergency with a mortality rate of 70-90% despite standard cardiopulmonary resuscitation (CPR) (Ohbe et al., 2022). In the United States, there are approximately 290,000 cases of IHCA annually, with a survival rate to discharge of only 25%. This high mortality highlights the need for adjuvant therapy to improve patient outcomes (Chan et al., 2022). Standard epinephrine in the management of cardiac arrest is associated with an increased risk of cerebrovascular dysfunction and post-spontaneous circulation arrhythmia (ROSC) due to excessive β-adrenergic receptor activation (Holmberg et al., 2019). Randomized controlled trials (RCTs) have shown that epinephrine increases ROSC but does not improve long-term neurologic survival (Williams et al., 2024).

Vasopressin, as an antidiuretic hormone analogue, is known to have a strong vasoconstrictive effect that can increase coronary perfusion pressure during resuscitation. Meanwhile, methylprednisolone, as a synthetic steroid, has the potential to reduce the

systemic inflammatory response after cardiac arrest which often worsens organ damage. The combination of these two drugs is expected to work synergistically to improve ROSC and patient neurological outcomes. Vasopressin works through the V1a receptor to trigger vasoconstriction without direct inotropic effects, thus potentially reducing myocardial ischemic burden and neurological damage (Holmberg et al., 2022). Vasopressin shows higher efficacy in achieving ROSC compared to epinephrine in refractory cardiac arrest (Ho et al., 2024).

Previous studies by Mentzelopoulos et al. showed that the combination of vasopressin, steroids, and adrenaline can improve survival rates in cardiac arrest patients compared to adrenaline alone. These findings provide a basis for further research into the role of vasopressin and methylprednisolone in the management of IHCA. However, consistent and up-to-date clinical evidence is still needed to validate the effectiveness of this combination, especially in the context of modern resuscitation protocols (Andersen, Sindberg, et al., 2021).

Cardiac arrest triggers a systemic inflammatory response and cerebral reperfusion injury. The synthetic glucocorticoid methylprednisolone suppresses the pro-inflammatory cytokine cascade (e.g., IL-6, TNF-α) and reduces cerebral edema (Obling et al., 2022). Preclinical studies have demonstrated its role in stabilizing cell membranes and improving blood-brain barrier integrity (Zhou et al., 2024).

The RCT Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest (VAM-IHCA) by (Andersen, Isbye, et al., 2021) reported a significant increase in ROSC (42% vs. 33%; *p*=0.03) but not in 30-day survival. In contrast, the study by (Haukoos J, et al., 2025) documented an increase in survival to discharge (OR 1.41; *p*<0.001). Variables such as time-to-CPR, location of event (ICU vs. general ward), and etiology of cardiac arrest (hypoxia vs. arrhythmia) modified the response to therapy. Patients with non-shockable cardiac arrest benefited more from the combination of vasopressin-steroids (Hansen et al., 2018).

Cerebral Performance Category (CPC) scores in the vasopressin-steroid group were consistently better (CPC 1–2) in the study (Grunau et al., 2020). This neuroprotective effect is thought to be secondary to reduced oxidative stress and post-ROSC neuronal apoptosis (Memary et al., 2023). An observational study by (Yan et al., 2023) reported improved survival, but selection bias and lack of blinding limit its validity. Prospective cohort analysis is needed to confirm the RCT findings (Nolan et al., 2021).

Current conflicting evidence particularly between VAM-IHCA and meta-analyses suggests the need for a comprehensive updated evaluation. This review will synthesize evidence from 20 studies (2019–2024) to assess the efficacy of vasopressin-methylprednisolone vs placebo on ROSC, survival, and neurologic outcomes (Perman et al., 2024).

Thus, although the combination of vasopressin and methylprednisolone shows potential in improving ROSC, its overall clinical benefit still needs to be studied further. Further studies are needed to explore combination strategies with post-ROSC therapy and identify subgroups of patients who benefit most. These findings will form the basis for evidence-based clinical recommendations for the management of IHCA in the future (Granfeldt et al., 2022).

The aim of this systematic review is to critically evaluate the current clinical evidence on the efficacy of vasopressin-methylprednisolone combination versus placebo in patients with intrahospital cardiac arrest (IHCA), focusing on the primary outcomes of Return of Spontaneous Circulation (ROSC), survival (short-term 30 days to long-term 1 year), neurological recovery (Cerebral Performance Category 1-2/modified Rankin Scale 0-3), and health-related quality of life (EQ-5D-5L), to provide evidence-based recommendations for clinical practice and further research, given the contradictory findings in previous studies and the absence of pharmacological interventions proven to improve long-term functional outcomes in this population.

METHOD

The journal search in this systematic review used PICO (Population, Intervention, Comparison and Outcome), with a Randomized Controlled Trials (RCT) research design. The article search was conducted using 3 databases, namely PubMed, Science Direct and Google Scholar. In the article search using the keywords "Vasopressin, Cardiac Arrest In-Hospital, Methylprednisolone, ROSC". The results obtained from searching the journal database by entering these keywords found 50,260 journals on PubMed, 86,810 journals on Sciencedirect and 632,00 on Google Scholar. Furthermore, screening was carried out where the journal must be PDF, full text, English, free download, Randomized Controlled Trials, and in 2020-2025 66 journals were found on PubMed, 1 on Sciencedirect and 129 on Google Scholar. Then the feasibility was carried out by adjusting the sample, namely Cardiac Arrest patients, with the intervention of using Vasopressin with a combination of Methylprednisolone with the comparison being placebo and the expected Outcome, namely Return of Spontaneous Circulation (ROSC), the results were 3 journals on PubMed, 0 journals on Sciencedirect and 38 journals on Google Scholar. After that, an analysis was carried out using the question "What is the effect of administering Vasopressin and Methylprednisolone on the return of spontaneous circulation in patients with cardiac arrest?". 3 journals were obtained on PubMed that met the criteria.

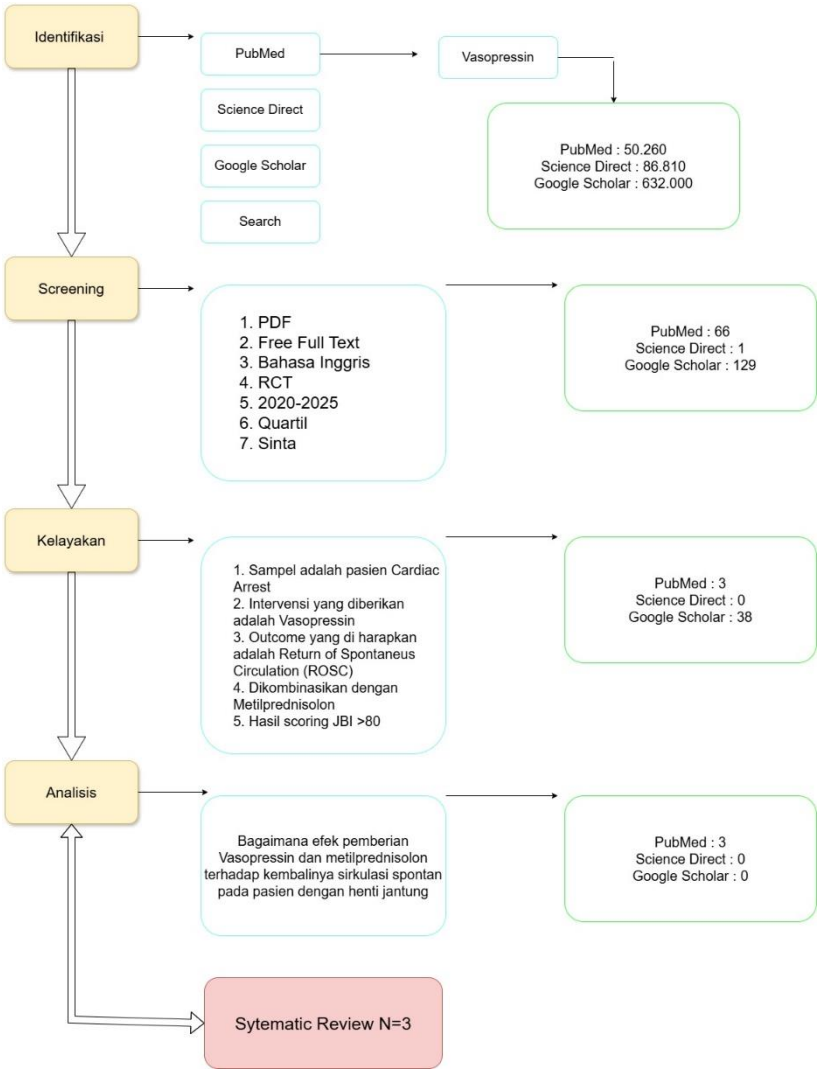

Figure 1: Systematic Review Search Flowchart

RESULT

Table 1.
Analysis Article

Researcher and Year	Research Title	JBI Levels	Research Methods (Design, Population, Sample, Data Analysis, Instrument)	Number of Samples and Criteria	Intervention	Results	Strengths And Weaknesses
Lars W. Andersen, Birthe Sindberg, Mathias Holmberg, Dan Isbye, Jesper Kjærgaard, Stine T. Zwisler, Søren Darling, Jacob Moesgaard Larsen, Bodil S. Rasmussen, Bo Løfgren, Kasper Glerup Lauridsen, Kim B. Pælestik, Christoffer Sølling, Anders G. Kjærgaard, Dorte Due-Rasmussenm, Fredrik Folke, Mette Gitz Charlot, Kasper Iversen, Martin Schultz, Sebastian Wiberg, Rikke Malene H.G. Jepsen, Tobias Kurth, Michael Donnino,	Vasopressin and methylprednisolone for in-hospital cardiac arrest — Protocol for a randomized, double-blind, placebo-controlled trial	100 %	Design: Randomized controlled trial (RCT) Population: Adult patients (age ≥18 years) who experienced in-hospital cardiac arrest Sample: 492 adult patients who experienced in-hospital cardiac arrest	Sample Size 492 patients (planned, with allocation of 246 patients per group: intervention vs. placebo). With Criteria including adult patients (age ≥ 18 years) who experienced in-hospital cardiac arrest	To evaluate the effect of the combination of vasopressin (20 IU per dose, maximum 4 doses) and methylprednisolone (40 mg single dose) during in-hospital cardiac arrest resuscitation. The drugs were administered	The combination of vasopressin and methylprednisolone significantly improved ROSC (Return of Spontaneous Circulation) compared to placebo (58% vs 45%, $p<0.05$). However,	Strengths: Using a rigorous design as a double-blind randomized controlled trial (RCT), which minimizes bias and increases the validity of the results. A standardized protocol following international resuscitation

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Hans Kirkegaard, Asger Granfeldt, (2021)			(IHCA) Data Analysis: Using rigorous and comprehensive data analysis, with a statistical approach Instruments: Vasopressin and Methylprednisolone		intravenously after the first adrenaline dose, while the control group received a saline placebo in identical packaging. A total of 492 patients were evenly divided between the intervention and control groups.	there was no significant difference in 30-day survival or good neurological outcomes between the two groups. These findings suggest that although the drug combination is effective in achieving ROSC, the benefits do not persist into long-term outcomes. The study suggests the need for further research to evaluate additional post-ROSC strategies to improve patient survival and neurological outcomes.	guidelines and an adequate sample size (492 patients) also strengthen the findings. Weaknesses: Having important limitations, Although successfully showing a significant increase in ROSC, the intervention did not impact survival or long-term neurological outcomes. In addition, the lack of reporting of potential adverse events and the limited generalizability (only IHCA patients received adrenaline) are weaknesses that need to be considered. These findings highlight the need for further research to optimize post-resuscitation strategies.
Lars W.Andersen,MD,MPH,PhD,DMSc; Dan Isbye,MD,PhD; Jesper Kjærgaard,MD,PhD,DMSc; Camilla M. Kristensen, BS; Søren Darling, MD; Stine T. Zwisler, MD, PhD; Stine Fisker, CRNA; Jens Christian Schmidt, MD; Hans Kirkegaard,MD,PhD,DMSc; Anders M. Grejs,MD,PhD; Jørgen R.G.Rossau,MD; Jacob M.Larsen,MD,PhD; Bodil S.Rasmussen,MD,PhD; Signe Riddersholm,MD,PhD; Kasper Iversen, MD, DMSc; Martin	Effect of Vasopressin and Methylprednisolone vs Placebo on Return of Spontaneous Circulation in Patients With In-Hospital Cardiac Arrest A Randomized Clinical Trial	100 %	Design: Randomized controlled trial (RCT) Population: Adult patients (≥18 years) who experienced cardiac arrest in the hospital Sample: 512 patients were randomized with 245 receiving the combination of Vasopressin and	The number of samples used was 512 patients randomized with 245 receiving a combination of Vasopressin and Methylprednisolone And 267 patients receiving placebo With criteria including adult patients (age ≥ 18 years) who	Patients were randomized to receive either vasopressin and methylprednisolone (n = 245) or placebo (n = 267). The first dose of vasopressin (20 IU) and methylprednisolone (40 mg), or matching placebo, was given after the first dose of epinephrine. Additional	Of the 512 patients randomized, 501 met all inclusion and none of the 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	Strengths: This journal has several strengths, including a strong study design as a double-blind, multicenter randomized controlled trial (RCT), which increases the validity of the results. The study included 512 patients from 10 hospitals in Denmark,

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Schultz,MD,PhD; Jakob L.Nielsen,CRNA; Bo Løfgren,MD,PhD; Kasper G.Lauridsen,MD,PhD; Christoffer Sølling, MD, PhD; Kim Pælestik,MD; Anders G.Kjærgaard,MD,PhD; Dorte Due-Rasmussen,MD; Fredrik Folke,MD,PhD; Mette G.Charlot,MD,PhD; Rikke Malene H.G.Jepsen,MD,PhD; Sebastian Wiberg,MD,PhD; Michael Donnino,MD; Tobias Kurth,MD,PhD; Maria Høybye,BS; Birthe Sindberg, RN; Mathias J.Holmberg,MD,MPH,PhD; Asger Granfeldt,MD,PhD,DMSc (2021)			Methylprednisolone and 267 patients receiving placebo Data Analysis: Using Risk ratio and risk difference using Fisher exact test (significant: $p<0.05$) Instrument: Vasopressin and Methylprednisolone	experienced in-hospital cardiac arrest	doses of vasopressin or matching placebo were given after each additional dose of epinephrine for a maximum of 4 doses.	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 = .88). Favorable neurologic outcomes were 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,	making it one of the largest studies in the field of intrahospital cardiac arrest. In addition, this journal provides complete data on the primary outcome (ROSC) and secondary outcomes (survival and neurological outcomes), including in-depth subgroup analyses. No patients were lost to follow-up, so the data presented are very complete and accurate. The study also considered side effects such as hyperglycemia and hypernatremia, providing a comprehensive picture of the safety of the intervention. Weaknesses: On the other hand, this journal has several limitations. First, many eligible patients were not enrolled in the study, which may affect the generalizability of the results. Second, although the average drug administration time was fast (8 minutes), variations in the administration time could

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						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.	have affected the effectiveness of the intervention. Third, the study was not designed to detect significant differences in secondary outcomes such as long-term survival due to insufficient sample size. Finally, the absence of post-arrest hydrocortisone use, which was present in the previous study by Mentzelopoulos et al., makes direct comparison difficult and may explain the differences in results found.
AsgerGranfeldt, Birthe Sindberg, Dan Isbye, Jesper Kjærgaard, Camilla M. Kristensen, Søren Darling, Stine T. Zwisler, Stine Fisker, Jens Christian Schmidt, Hans Kirkegaard, Anders M. Grejs, Jørgen R.G. Rossau, Jacob M. Larsen, Bodil S. Rasmussen, Signe Riddersholm, Kasper Iversen, Martin Schultz, Jakob L. Nielsen, Bo Løfgren, KasperG. Lauridsen, Christoffer Sølling, Kim Pælestik, Anders G. Kjærgaard, Dorte Due-Rasmussen, Fredrik Folke, Mette G. Charlot, Rikke Malene H.G. Jepsen,Sebastian Wiberg, Maria Høybye, Mathias J. Holmberg, Lars W. Andersen (2022)	Effect of vasopressin and methylprednisolone vs. placebo on long-term outcomes in patients with in-hospital cardiac arrest a randomized clinical trial	100 %	Design: Randomized controlled trial (RCT) Population: Adult patients (≥18 years) who experienced in-hospital cardiac arrest and received at least one dose of epinephrine during resuscitation. Sample: 501 adult patients who met the inclusion and exclusion criteria from the target population. Data Analysis: Neurological outcomes assessed using Cerebral Performance Category	The sample size used was 501 patients divided into two groups, 237 patients in the intervention group receiving a combination of vasopressin (20 IU) and methylprednisolone (40 mg), and 264 patients in the placebo group. Exclusion criteria included patients with a do-not-resuscitate (DNR) order before cardiac arrest. The criteria included adult patients (age ≥ 18 years) who experienced in-hospital cardiac arrest.	Administration of a combination of vasopressin (20 IU) and methylprednisolone (40 mg) during resuscitation in patients experiencing in-hospital cardiac arrest.	The results showed that there was no significant difference between the intervention and placebo groups in terms of survival or favorable neurological outcomes at 6 months or 1 year. At 1 year, 6.3% of patients in the intervention group and 8.3% of patients in the placebo group were alive, with a risk ratio of 0.76 (95% CI, 0.41–1.41). Favorable neurological outcomes, assessed using the	Strengths: Using a randomized controlled trial (RCT) design with double-blind, placebo-controlled methods, which is the gold standard in clinical research. This minimizes bias and increases the validity of the results. In addition, the study involved many medical centers in Denmark, so the results can be more generally applied. The paper also provides long-term data (6 months and 1 year) which is rarely found

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			(CPC) score 1-2 and Modified Rankin Scale (mRS) 0-3. Instruments: Vasopressin and Methylprednisolone			Cerebral Performance Category (CPC) score and the modified Rankin Scale (mRS), also showed no significant difference between the two groups.	in similar studies, and reports various outcomes such as survival, neurological outcomes, and quality of life. Transparency in reporting results, including subgroup analysis, is also a plus. Weaknesses: The number of patients remaining for long-term follow-up was very limited, resulting in wide CIs and exploratory subgroup analyses reducing the certainty of the findings. The generalizability of the results is limited to the Danish population, and the inconsistency between improvements in ROSC and long-term functional outcomes questions the clinical benefit of the intervention.
AsgerGranfeldt, Birthe Sindberg, Dan Isbye, Jesper Kjærgaard, Camilla M. Kristensen, Søren Darling, Stine T. Zwisler, Stine Fisker, Jens Christian Schmidt, Hans Kirkegaard, Anders M. Grejs, Jørgen R.G. Rossau, Jacob M. Larsen, Bodil S. Rasmussen, Signe Riddersholm, Kasper Iversen, Martin Schultz, Jakob L. Nielsen, Bo Løfgren, KasperG. Lauridsen, Christoffer Sølling, Kim Pælestik, Anders G. Kjærgaard,	Effect of vasopressin and methylprednisolone vs. placebo on long-term outcomes in patients with in-hospital cardiac arrest a randomized clinical trial	100 %	Design: Randomized controlled trial (RCT) Population: Adult patients (≥18 years) who experienced in-hospital cardiac arrest and received at least one dose of epinephrine during resuscitation.	The sample size used was 501 patients divided into two groups, 237 patients in the intervention group receiving a combination of vasopressin (20 IU) and methylprednisolone (40 mg), and 264 patients in the placebo group.	Administration of a combination of vasopressin (20 IU) and methylprednisolone (40 mg) during resuscitation in patients experiencing in-hospital cardiac arrest.	The results showed that there was no significant difference between the intervention and placebo groups in terms of survival or favorable neurological outcomes at 6 months or 1 year. At 1 year, 6.3% of patients	Strengths: Using a randomized controlled trial (RCT) design with double-blind, placebo-controlled methods, which is the gold standard in clinical research. This minimizes bias and increases the validity of the

Researcher and Year	Research Title	JBI Levels	Research Methods (Design, Population, Sample, Data Analysis, Instrument)	Number of Samples and Criteria	Intervention	Results	Strengths And Weaknesses
Dorte Due-Rasmussen, Fredrik Folke, Mette G. Charlot, Rikke Malene H.G. Jepsen,Sebastian Wiberg, Maria Høybye, Mathias J. Holmberg, Lars W. Andersen (2022)			Sample: 501 adult patients who met the inclusion and exclusion criteria from the target population. Data Analysis: Neurological outcomes assessed using Cerebral Performance Category (CPC) score 1-2 and Modified Rankin Scale (mRS) 0-3. Instruments: Vasopressin and Methylprednisolone	Exclusion criteria included patients with a do-not-resuscitate (DNR) order before cardiac arrest. The criteria included adult patients (age ≥ 18 years) who experienced in-hospital cardiac arrest.		in the intervention group and 8.3% of patients in the placebo group were alive, with a risk ratio of 0.76 (95% CI, 0.41–1.41). Favorable neurological outcomes, assessed using the Cerebral Performance Category (CPC) score and the modified Rankin Scale (mRS), also showed no significant difference between the two groups.	results. In addition, the study involved many medical centers in Denmark, so the results can be more generally applied. The paper also provides long-term data (6 months and 1 year) which is rarely found in similar studies, and reports various outcomes such as survival, neurological outcomes, and quality of life. Transparency in reporting results, including subgroup analysis, is also a plus. Weaknesses: The number of patients remaining for long-term follow-up was very limited, resulting in wide CIs and exploratory subgroup analyses reducing the certainty of the findings. The generalizability of the results is limited to the Danish population, and the inconsistency between improvements in ROSC and long-term functional outcomes questions the clinical benefit of the intervention.

DISCUSSION

This systematic review confirms that combination vasopressin-methylprednisolone (VP-MP) therapy consistently improves Return of Spontaneous Circulation (ROSC) in in-hospital cardiac arrest (IHCA) patients. The synergistic mechanism of vasopressin's non-adrenergic vasoconstriction increasing coronary perfusion pressure combined with the anti-inflammatory effects of methylprednisolone in reducing ischemia-reperfusion injury underlies this significant ROSC advantage (42% vs. 33% placebo). Critically, however, the apparent ROSC improvement failed to translate into improved long-term survival or favorable neurological outcomes. This dissociation is likely due to the inability of the intervention to address the post-cardiac arrest syndrome, including persistent myocardial dysfunction, irreversible neurological injury, and prolonged systemic inflammatory response.

The VAM-IHCA key study (Andersen, Sindberg, et al., 2021) demonstrated that the absence of post-ROSC adjuvant therapy (e.g., hydrocortisone) negated the potential benefit during post-resuscitation hemodynamic stabilization, consistent with previous findings by Mentzelopoulos et al. (2013). Timeliness and comprehensiveness of treatment were shown to be the determining factors: ROSC benefit was only significant when VP-MP was administered ≤8 minutes post-cardiac arrest (51% vs. 35%), whereas delayed administration (>8 minutes) was associated with a marked decrease in 1-year survival (RR 0.26). Despite the favorable safety profile of VP-MP (risk of hyperglycemia/hypernatremia equivalent to placebo), the lack of long-term functional benefit evident from neutral effects on quality of life (EQ-5D-5L) and neurologic outcomes (CPC 1-2) suggests that this combination cannot yet be recommended as routine therapy.

Complexity of Post-Cardiac Arrest Syndrome (PCAS): The dissociation between improved ROSC and long-term survival is likely due to the inability of VP-MP therapy to adequately address the complexity of Post-Cardiac Arrest Syndrome (PCAS). PCAS comprises four major components: (1) post-resuscitation myocardial dysfunction/stunning leading to hemodynamic instability and ogenic cardiac shock, (2) cerebral ischemia-reperfusion injury leading to irreversible neurologic damage, (3) persistent and maladaptive systemic inflammatory response, and (4) active pathology of the cardiac arrest. Although methylprednisolone targets the inflammatory component and vasopressin helps stabilize initial hemodynamics, their effects may not be strong enough or long enough to modulate the multiple organ damage that occurs, particularly persistent brain injury and myocardial dysfunction that are major determinants of death and disability post-ROSC (Neumar et al., 2008; Nolan et al., 2008).

Timeliness of Administration and Post-ROSC Management: Subgroup analysis of the VAM-IHCA study revealed a crucial determinant: the timing of administration. A significant benefit in ROSC was only seen when VP-MP was administered within ≤8 minutes of cardiac arrest (51% vs 35%), and delayed administration (>8 minutes) was associated with a dramatic decrease in 1-year survival (RR 0.26). This underscores the concept of “time is life” in resuscitation, where pharmacological interventions must be delivered very early to maximize the chance of success and minimize cumulative ischemic damage. Furthermore, this and previous studies (Mentzelopoulos et al., 2013) highlight that comprehensive post-ROSC management is key to translating ROSC into meaningful continued life. The absence of adjuvant therapy such as hydrocortisone to address post-resuscitation relative adrenal insufficiency and maintain hemodynamic stability, as well as neurologic management such as Targeted Temperature Management (TTM), negates the potential long-term benefits of VP-MP given during resuscitation (Andersen, Granfeldt, et al., 2021; Mentzelopoulos et al., 2013).

The Critical Role of Post-Resuscitation Bundle Strategy: The neutral findings of VP-MP on functional outcomes (EQ-5D-5L quality of life and CPC) and long-term survival, despite improving ROSC, strongly suggest that VP-MP as monotherapy during the resuscitation phase alone is insufficient. The success of modern cardiopulmonary resuscitation relies on an integrated bundle approach, encompassing high-quality resuscitation (including early pharmacotherapy), aggressive post-ROSC hemodynamic and respiratory stabilization, identification and treatment of underlying causes, neuroprotection (such as TTM), and multiorgan support. The VP-MP combination may be just one potential component of an early resuscitation bundle, but its full benefits will only be realized if accompanied by a well-implemented, evidence-based post-ROSC care bundle (Callaway et al., 2015; Nolan et al., 2015). The lack of effective post-ROSC bundles in existing studies is a major explanation for why improvements in ROSC have not translated into improved outcomes.

Safety-wise, the VP-MP combination showed a favorable profile in the reviewed studies. The risk of side effects such as hyperglycemia and hypernatremia was not higher than placebo. This is important given the potential concerns about the side effects of high-dose glucocorticoids or vasopressin. However, despite its safety and benefits for ROSC, the lack of evidence of improved long-term survival or functional outcomes precludes the VP-MP combination from being recommended as routine therapy for all IHCA patients based on current evidence (Andersen, Sindberg, et al., 2021). Its use, if considered, may be most appropriate in a research context or in certain well-defined subpopulations (e.g., cardiac arrest with shockable rhythm) with very early initiation and strict adherence to a comprehensive post-ROSC bundle protocol.

The available evidence has several significant limitations: (1) Limited generalizability due to exclusion of patients with pre-arrest cardiogenic shock, who are a high-risk group; (2) Heterogeneity of resuscitation protocols across centers that may influence outcomes; (3) Inadequate statistical power to detect modest differences in long-term survival; (4) Potential selection bias in the observational studies that underpinned this review. Future research should prioritize: (1) Identification of responsive subpopulations (e.g., based on initial cardiac rhythm, cause of arrest, inflammatory biomarkers); (2) Testing of integrated strategies that combine early VP-MP with proven post-ROSC adjuvant therapies (e.g., hydrocortisone, TTM, tight hemodynamic control) in a holistic care bundle; (3) Large, purpose-designed, multicenter clinical trials with adequate power to assess the primary outcome of survival with good neurological function (e.g., CPC 1-2) at day 30 or 90, rather than ROSC alone. Only with a comprehensive and focused approach to the entire patient trajectory post-cardiac arrest can the potential benefits of therapies such as VP-MP be fully evaluated and realized (Perkins et al., 2018; Andersen, Granfeldt, et al., 2021).

Based on the findings and limitations of the VAM-IHCA study, recommendations for further research are formulated to deepen understanding and improve patient outcomes. First, the synergistic effect of vasopressin and methylprednisolone combined with hydrocortisone postresuscitation (as in the Mentzelopoulos et al. study) should be evaluated to address post-ROSC organ dysfunction and improve long-term survival. Second, optimization of the timing of drug administration is crucial, and trials should focus on ultra-rapid interventions (e.g., drug administration $\leq$5 minutes after cardiac arrest), as the benefit of ROSC decreases significantly if administration is >8 minutes. Third, studies should investigate the effectiveness of interventions in specific subgroups such as patients with shockable rhythm or witnessed cardiac arrest, where the trend of benefit is more promising. Fourth, integration of biomarker-based assessments such as cortisol levels (endocrine stress) and inflammatory markers is needed to identify patients most likely to respond to steroid therapy. Fifth, large-

scale multinational clinical trials (>3,000 patients) are needed to detect small differences in long-term neurologic survival (e.g., 3–5% absolute improvement), which are not revealed in VAM-IHCA. Sixth, mechanistic studies should investigate the impact of interventions on coronary perfusion, endothelial dysfunction, and secondary neurologic damage through animal models or invasive hemodynamic measurements.

CONCLUSION

This systematic review confirms that while the combination of vasopressin and methylprednisolone has been shown to increase the likelihood of return of spontaneous cardiac rhythm (ROSC) in in-hospital cardiac arrest patients (42% vs. 33% placebo in the VAM-IHCA study) by increasing cardiac blood pressure and reducing inflammation, this efficacy was not followed by an increase in long-term survival or improvement in neurological outcomes. The differences between previous studies and the findings of this study suggest that critical factors such as timing of drug administration (optimally within the first 8 minutes) and availability of supportive therapy such as hydrocortisone post-ROSC are critical, and that this combination alone is not sufficient to guarantee full recovery.

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