Effect of Vasopressin and Methylprednisolone vs Placebo on Return of Spontaneous Circulation in Patients with In-Hospital Cardiac Arrest

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Background:
Clinical trials are sparse in the setting of cardiac arrest, especially In-hospital Cardiac Arrest (IHCA). Not only is there scarcity of evidence behind many of the pharmacological interventions used in cardiac arrest, most, if not all evidence has been extrapolated from Out-of-hospital Cardiac Arrest (OHCA) trials. A previous set of trials, the VSE trials in 2009 and 2013, were conducted by a research group in Greece to assess the addition of Vasopressin and Methylprednisolone to the standard of care in cardiac arrest. The 2013 VSE trial found the addition of vasopressin and corticosteroids to standard epinephrine during cardiopulmonary resuscitation to improve rates of ROSC with 18% more patients having Return of Spontaneous Circulation lasting longer than 20 minutes (NNT 5). They also found that 8.8% more patients in the intervention group had survival to discharge with favorable neurological outcomes (NNT 11). Both the International Liaison Committee on Resuscitation (ILCOR) and the American guidelines acknowledged the potential of these agents but called for further study.

What They Did:
- Conducted within 10 hospitals in Denmark, patients were recruited between October 15, 2018 - January 21, 2021.
- A total of 512 adult patients with IHCA were included in this randomized, placebo-controlled, parallel group, double-blind superiority trial.
- Patients were randomized in a 1:1 fashion to receive 40mg Methylprednisolone and 20IU vasopressin given immediately after first dose of epinephrine or placebo.
- Further doses of vasopressin (20IU, to a maximum 4 doses) could be given after each further epinephrine doses.
- Identical ampules of 0.9% Sodium chloride used as control and the trial drugs were brought to the patient in a blinded study kit by a dedicated member of the clinical cardiac arrest team.

Outcomes:
- Primary: Return of Spontaneous Circulation (ROSC) lasting longer than 20 minutes
- Secondary: Survival at 30 or 90 days, Favorable neurological outcome at 30 or 90 days

Inclusion:
- Patients ≥ 18 years old
- IHCA
- Received at least 1 dose of epinephrine

Exclusion:

- Valid DNR order
- Prior enrollment in trial
- Invasive circulatory support
- Known or suspected pregnancy

Results:

- Primary outcome of ROSC:
  - 100 (42%) in Vasopressin/Methylprednisolone group
  - 86 (33%) in placebo group
- 30 d survival:
  - 23 (9.7%) in Vasopressin/Methylprednisolone group
  - 31 (12%) in placebo group
- 90 d survival:
  - 20 (8.4%) in Vasopressin/Methylprednisolone group
  - 24 (9.1%) in placebo group
- 30 d favorable neurologic outcome (CPC 1,2):
  - 18 (7.6%) in Vasopressin/Methylprednisolone group
  - 20 (7.6%) in placebo group
- 90 d favorable neurologic outcome (CPC 1,2):
  - 18 (7.6%) in Vasopressin/Methylprednisolone group
  - 20 (7.6%) in placebo group
- 30 d favorable neurologic outcome (mRS 0-3)
  - 11 (4.6%) in Vasopressin/Methylprednisolone group
  - 19 (7.2%) in placebo
- 90 d favorable neurologic outcome (mRS 0-3)
  - 15 (6.3%) in Vasopressin/Methylprednisolone group
  - 20 (7.6%) in placebo group
- Safety Outcomes: Vasopressin/methylprednisolone vs. placebo
  - Hyperglycemia: 77% v 73%
  - Hypernatremia: 28% v 31%
  - Pneumonia: 21% v 17%
  - GI bleeding: 5% v 3%

Strengths:

- Large trial in a logistically challenging study area
- Strong internal validity: multicenter, double-blinded, good randomization, pre-published protocol, similar baseline characteristics
- Sensible primary outcome of ROSC
- Strong adherence to protocol
- Long term outcomes obtained without loss to follow-up

Limitations:

- Performed in only one country

- Possible selection bias, 170 of patients screened excluded due to “physician preference” and 193 due to “team forgot”
- Overall survival appears low, possibly because of epinephrine administration as inclusion criteria
- The trial was not powered for the survival or neurologic outcomes; thus, the results cannot rule out potential harm or benefit
- Higher rates of extracorporeal support in placebo group

Discussion:

- Author’s conclusion: “The administration of vasopressin and methylprednisolone, compared to placebo, significantly increased the likelihood of return of spontaneous circulation. However, uncertainty remains as to whether this treatment results in long term survival benefit.”
- Clinical take home point: Neither vasopressin or methylprednisolone are currently guideline recommended in the setting of ACLS. However, because there is not an incredible amount of data behind some of the agents currently used in cardiac arrest, this potential benefit of increased rates of ROSC with these agents is certainly promising given the fact that ROSC is a prerequisite for more long-term survival.

References:

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