Journal Club Synopsis
Block 6, November 26, 2013
Discussion Leader: Alan Dupre, MD
Host: Glenn Burns, MD

Does VSE during ACLS increase the chances of neurologically favorable survival?

Clinical Scenario: On a spooky October day while working at MVH and looking forward to all of the zombies and goblins that were headed your way, you are called to run a code of a gentleman who collapsed without pulses while visiting a patient. After following ACLS protocols, you have return of spontaneous circulation and move on to post-resuscitative care and admission. Later that night, you hear a podcast about the "VSE combination" (vasopressin, steroids, epinephrine) in cardiopulmonary resuscitation recently published in JAMA. You begin to wonder if in-hospital or out-of-hospital adult cardiac arrest patients would achieve better survival (or more importantly neurologically favorable survival) if treated with this new VSE protocol.

Article 1: Effect of Adrenaline on Survival in Out-of-Hospital Cardiac Arrest: A Randomized Double-blind Placebo-controlled Trial. Jacobs, Ian, et al. *Resuscitation.* 2011; 82: 1138-1143.

This is the first known human double-blind, randomized, placebo-controlled study evaluating the current ACLS recommendation of epinephrine in pulseless arrest. The study was performed in out-of-hospital arrests with 534 patients being randomized to either epinephrine or normal saline. Patients were well matched for baseline characteristics. Of patients receiving epinephrine, 23.5% achieved ROSC, but only 4% survived to hospital discharge. In the placebo group, 8.4% achieved ROSC with 1.9% surviving to hospital discharge. The study was underpowered, but is consistent with other studies' findings in showing that epinephrine significantly improves likelihood of achieving ROSC and short-term survival, but has no statistically significant improvement in long-term survival. This study most closely resembles the patient population that is frequently encountered in the ED, and was discussed as an illustration of limitations to current therapy. Journal club participants discussed whether the goals of resuscitation should be short-term or long-term survival. While most agree that long-term survival is the ideal goal, some participants pointed out that short-term survival may have desirable effects in allowing family members to have time with the patient before death or in allowing other post-resuscitative interventions to effect long-term survival.

Article 2: Vasopressin, Epinephrine, and Corticosteroids for In-Hospital Cardiac Arrest. Mentzelopoulos, Spyros, et al. Arch Internal Med. 2009; 169 (1): 15-24.

This study is a 100 patient single center, prospective, randomized, double-blind, placebo-controlled, parallel group trial evaluating a novel resuscitation protocol

involving vasopressin, steroids, epinephrine (VSE) in in-hospital arrest patients. Study patients received vasopressin (20 IU) and epinephrine (1 mg) per resuscitation cycle for the first 5 cycles with 40 mg of methylprednisolone being given in the first resuscitation cycle and with post-resuscitation shock being treated with a maximum of 7 days of daily hydrocortisone (300 mg). Control patients received epinephrine (1 mg) with each resuscitative cycle plus saline placebo given with each dose of epinephrine and normal saline placebo given each day of post-resuscitative shock. The majority of patients were found with an initial rhythm of asystole or PEA. Of study group patients, 81% of patients had ROSC and 19% survived to hospital discharge compared to 52% and 4%, respectively, in the control group. Additionally, there were statistically significant differences in the groups in other potentially important factors. The study group had higher systolic arterial and mean arterial pressures during CPR and after ROSC. Study participants also showed improved venous oxygen saturations and more organ failure free days. Adverse events were similar between the two groups. The authors conclude that the VSE protocol may improve long-term survival by a factor of 4.5. This study was well designed with excellent patient follow-up and impressive results; however, the study sample was small and involves in-hospital arrests that may not apply to predominantly out-of-hospital arrests seen in the ED. Additionally, this study could not evaluate the neurologic outcome associated with the long-term survival.

Article 3: Vasopressin, Steroids, and Epinephrine and Neurologically Favorable Survival After In-Hospital Cardiac Arrest: A Randomized Clinical Trial. Mentzelopoulos, Spyros, et al. JAMA. 2013; 310 (3): 270-279.

This article is a multi-center, randomized, double-blind, placebo-controlled, parallel group trial involving 268 patients with in-hospital cardiac arrest evaluating the VSE protocol described in article #2 vs placebo plus epinephrine. The study protocol was identical to article #2 above, but was powered to evaluate ROSC and survival to hospital discharge with a CPC score of 1 or 2. The authors found VSE study group patients had a statistically significant higher probability of ROSC (83.9% vs 65.9% in the placebo group) and hospital discharge with CPC 1-2 (13.9% vs 5.1% in the placebo group). This correlates with an odds ratio of 2.98 for ROSC and 3.28 for neurologically favorable survival with a NNT=11. Findings of improved hemodynamics, central venous oxygenation, and organ failure free days in the study group were similar to findings in article #2. It was noted that study group patients in this study received less epinephrine and had shorter ACLS duration. Again, this study enrolled a relatively small sample of patients with in-hospital arrest with questionable applicability to ED patients. This is a second study with impressive results, to include favorable neurologic survival, but this study was performed by the same author as article #2. So far, there has been no independent validation study performed.

Synopsis:

Current management of cardiac arrest leaves much to be desired in terms of outcomes. The AHA/ACC 2010 guidelines recognize that, “Although there is evidence

that vasopressor (epinephrine or vasopressin) may improve ROSC and short-term survival, there is insufficient evidence to suggest that vasopressors improve survival to discharge and neurological outcome." Two recent studies by the same author propose a novel approach to resuscitative care using vasopressin, steroids, epinephrine. While the studies were well-designed with good followup, and with impressive results, both in terms of long-term survival and neurologically favorable survival, there is concern that both studies were performed with relatively small sample sizes by the same author with no independent validation study. An extensive literature search for both trade and generic names of prednisone, dexamethasone, methylprednisolone, hydrocortisone, as well as vasopressin and epinephrine did not reveal any other studies using these medications in combination. There were, however, multiple studies, some of which supplied as background articles for this journal club, studied steroids, vasopressin, epinephrine, individually in resuscitative care. None of these components were found individually to provide any statistically significant benefit to long-term survival or neurologically favorable outcome. It is possible that the combination would provide some benefit not achieved individually by the components; however, additional validation studies are needed to confirm the benefits shown by this author's studies. Additional studies are needed in out-of-hospital arrest as well to confirm benefit in a typical ED population. After reading the articles, journal club participants were asked to indicate whether they would use the new VSE protocol. At that time 67% of attendees said they would be interested in trying the new protocol. After the group discussion, attendees were polled again, and this time, only 43% were interested in using the protocol at this time.

Bottom Line:

The two studies discussed show promise for the VSE protocol in an in-hospital arrest scenario. However, additional validation studies are needed before the proposed benefit can be confirmed, especially in an ED population.