January 2015

Washington University Emergency Medicine Journal Club
Epinephrine in Out-of-Hospital Cardiac Arrest

Vignette

You are doing an EMS ride-along during your EMS elective and get a call for a 70-year old male in cardiac arrest. The paramedic hits the lights and sirens and you're on scene in five minutes. The fire department has already arrived and CPR is in progress. They tell you that the patient was watching TV with his wife when he collapsed about 15 minutes prior to their arrival. He did not receive any bystander CPR and was pulseless and apneic on their arrival.

You and the EMS team take over CPR and bag the patient while hooking up the monitor. He is found to be in asystole and the paramedic grabs an amp of epinephrine. You place a supraglottic airway, he gets the epinephrine, and you load him up while continuing good, uninterrupted chest compressions. He gets two more rounds of epi en route and gets a pulse back.

On arrival to the ED he has a pulse, is mildly hypotensive, but has no spontaneous breaths and his pupils are fixed and dilated. You know that giving epinephrine in cardiac arrest is the standard of care, but wonder what effect it really has: does it improve ROSC, and if so does it actually improve neurologic function down the road. You wonder if their is really any evidence to support its use at all. You head to the computer and start searching...

PICO Question
Population: Adult patients with atraumatic out-of-hospital cardiac arrest
Intervention: Intravenous epinephrine administration
Comparison: Standard CPR without epinephrine administration
Outcome: Return of spontaneous circulation, survival to hospital admission, survival to hospital discharge, survival with a good neurologic outcome

Search Strategy

A PubMed search was performed using the search terms "(out of hospital cardiac arrest) AND (epinephrine OR adrenaline)." The search was limited to humans, resulting in 207 citations (http://tinyurl.com/lsgy63r). These were searched and two randomized controlled trials, one observational trial, and a systematic review were chosen for inclusion.

Article 1: Reardon PM, Magee K. Epinephrine in out-of-hospital cardiac arrest: A critical review. World J Emerg Med. 2013;4(2):85-91. Answer Key.

Article 2: Jacobs IG, Finn JC, Jelinek GA, Oxer HF, Thompson PL. Effect of adrenaline on survival in out-of-hospital cardiac arrest: A randomised double-blind placebo-controlled trial. Resuscitation. 2011 Sep;82(9):1138-43. Answer Key.

Article 3: Olasveengen TM, Sunde K, Brunborg C, Thowsen J, Steen PA, Wik L. Intravenous drug administration during out-of-hospital cardiac arrest: a randomized trial. JAMA. 2009 Nov 25;302(20):2222-9. Answer Key.

Article 4: Hagihara A, Hasegawa M, Abe T, Nagata T, Wakata Y, Miyazaki S. Prehospital epinephrine use and survival among patients with out-of-hospital cardiac arrest. JAMA. 2012 Mar 21;307(11):1161-8. Answer Key.

Bottom Line

Epinephrine is currently recommended in the management of out-of-hospital cardiac arrest (OHCA) by both the American Heart Association and the European Resuscitation Council despite a paucity of clear evidence that it improves patient-centered outcomes. This lack of evidence has led some clinicians to question the use of epinephrine in cardiac arrest. The primary proposed benefit of epinephrine has been an increase in coronary perfusion pressure, which has been demonstrated in animal studies. While no placebo-controlled human studies have confirmed these findings, high-dose epinephrine has been shown to increase coronary perfusion to an even greater extent than low-dose epinephrine. However, this dose-response relationship does not necessarily confirm the benefits of epinephrine. While high-dose epinephrine has been shown to improve rates of return of spontaneous circulation (ROSC), it does not improve the more clinically relevant outcome of survival to hospital discharge (Gueugniaud 1998, Vandycke 2000). This may be in part due to reduced microcirculatory cerebral blood flow caused by epinephrine, resulting in worse neurologic outcomes among survivors.

There have been several observational studies evaluating the use of epinephrine in OHCA with varying results (Herlitz 1995, Holmberg 2002, Ohshige 2005, Wang 2005, Ong 2007, Yanagawa 2010). The largest of these studies (Hagihara 2012) prospectively evaluated outcomes in over 400,000 patients in Japan. The authors found that while epinephrine use was associated with a significant increase in ROSC (adjusted odds ratio [AOR] 2.01, 95% CI 1.83-2.21), it was also associated with significant decreases in survival at one month (AOR 0.71, 95% CI 0.62-0.81) and survival with good neurologic function, as defined by a cerebral performance category (CPC) score of 1 or 2 (AOR 0.41, 95% CI 0.33-0.52).

There has been, to date, one randomized controlled trial comparing the use of epinephrine with placebo in the management of OHCA (Jacobs 2011). While this study demonstrated improvements in survival to hospital discharge with the use of epinephrine, this result did not achieve statistical significance (OR 2.2, 95% CI 0.7-6.3). The study was afflicted, unfortunately, by a small sample size and was underpowered to detect a potentially clinically significant improvement in outcomes. While the investigators initially planned to perform a large study involving five ambulance services throughout Australia and New Zealand, all but one service withdrew from the study due to ethical concerns.

There has been an additional randomized controlled study evaluating the effectiveness of intravenous drug administration during cardiac arrest (Olasveengen 2009), of which epinephrine is arguably the most important component. This study also demonstrated higher rates of ROSC among patients with IV access initiated by EMS (OR 1.99, 95% CI 1.48-2.67). However, there was no statistically significant improvement in survival to discharge (OR 1.16, 95% CI 0.74-1.82) or survival with a CPC score of 1 or 2 (OR 1.24, 95% CI 0.77-1.98). There was a large degree of crossover in this study, and the authors chose to perform an "as treated" analysis of the data based on epinephrine administration (Olasveengen 2012). This analysis demonstrated a significant decrease in both survival to discharge (OR 0.5, 95% CI 0.3-0.8) and survival with a CPC score of 1 or 2 (OR 0.4, 955 CI 0.2-0.7) when epinephrine was administered. These results must be viewed cautiously, as the reasons for crossover between the groups likely disrupted the prognostic balance afforded by randomization, leading to a poorer baseline prognosis among patients receiving epinephrine. Note that among 418 patients randomized to receive an IV, 42 did not have IV access initiated because they had ROSC; only 12 patients in this group did not have IV access initiated due to futility. Among 433 patients randomized to have no IV access initiated, 27 received IV access only after having ROSC and then rearresting.

The existing data is clearly limited, and the authors of a systematic review on the subject understandably conclude that "although the results…exhibit the paucity of high quality published research supporting the use of epinephrine in OHCA, there is insufficient evidence to support changing current guidelines" (p. 90). Fortunately, a trial has recently begun in the United Kingdom (PARAMEDIC 2: the Adrenaline Trial) which plans to enroll 8000 patients randomized to either epinephrine or placebo. This trial will hopefully further elucidate the efficacy or harm associated with epinephrine and provide statistically significant outcomes data to solidify or change our current practice.