ORIGINAL RESEARCH

Comparison of Two Protocols for Pulseless Cardiopulmonary Arrest: Vasopressin Combined with Epinephrine Versus Epinephrine Alone

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Keywords: cardiopulmonary arrest; epinephrine; vasopressin

Abbreviations:
AHA = American Heart Association
CPR = cardiopulmonary resuscitation
EMS = emergency medical services
ROSC = return of spontaneous circulation

Received: 26 October 2009
Accepted: 02 December 2009
Revised: 15 December 2009

Web publication: 20 September 2010

Abstract

Introduction: Survival from pulseless cardiac arrest typically is dismal. Some suggest that adding vasopressin to epinephrine as a cardiovascular stimulant can improve outcomes.

Problem: This study compares survival outcomes using epinephrine verses vasopressin and epinephrine in persons with pulseless cardiac arrest.

Methods: This is a retrospective, cohort evaluation of two resuscitative protocols (P1-epinephrine or P2-vasopressin with epinephrine) in a tiered response, community emergency medical service (EMS) with an approximately 100,000 catchment area. Cases are defined as 18 years or older determined to be in pulseless cardiac arrest. Outcomes were survival to emergency department arrival, to 24 hours, and to hospital discharge. Data were entered into Microsoft Office Excel® and processed using Analyze-it® for continuous and categorical data and Epi-Info® for odds ratios with confidence intervals.

Results: There were 204 cases (60.3% males and 39.7% females) who met the inclusion criteria. Thirteen cases received electrical therapy only, and were dropped from analysis, leaving 191 (93.6%) who were included in the study; P1 to 85 (44.5%) and P2 to 106 (55.5%). Younger age was associated with improved survival to discharge home in both protocols, $p = 0.003$ (95% CI = 0.004–0.010). No difference in survival was noted at the levels of emergency department arrival OR 1.42 (95% CI = 0.73, 2.76) $p = 0.26$; 24 hour survival OR 0.54 (95% CI = 0.22–1.30) $p = 0.133$, or discharge home OR = 1.81 (95% CI = 0.49–6.88) $p = 0.319$.

Conclusions: This study in a community EMS did not demonstrate improved survival with the addition of vasopressin to epinephrine for pulseless cardiac arrest.

Cody P, Lauderdale S, Hogan DE, Frantz RR: Comparison of two protocols for pulseless cardiopulmonary arrest: Vasopressin combined with epinephrine versus epinephrine alone. *Prehosp Disaster Med* 2010;25(5):420–423.

Introduction

Survival from pulseless cardiac arrest under most conditions is dismal—about 6% in the United States.[1] The incidence of hospital discharge after cardiac arrest with neurologic competency is difficult to evaluate due to low cardiac arrest survival to hospital discharge.[2] Historically, resuscitative protocols have called for the use of epinephrine as the primary cardiovascular stimulant in pulseless cardiac arrest. However, some authors recently have suggested benefit with the addition of vasopressin in combination with epinephrine in this setting.[3]

Importance

Such recommendations are primarily based on studies performed in large emergency medical services (EMS) systems or inpatient settings.[4–10] In addition, there are a number of contradictory studies both supporting and not supporting benefit with the addition of vasopressin in the setting of pulseless cardiac arrest.

Goals

This study was conducted to compare survival outcomes associated with the use of two resuscitative protocols by a community EMS system for out-of-hos-

pital pulseless cardiac arrest, one protocol using epinephrine, the other using vasopressin in addition to epinephrine.

Methods

This study was a retrospective, cohort evaluation of two resuscitative protocols. The study population consists of approximately 100,000. The prehospital EMS for the community is a hospital-based ambulance service operated through the 9-1-1 emergency telephone system, with a tiered response of first responders from the local fire department and paramedics from the ambulance service. All cases transported, were taken to the same regional hospital staffed by board certified emergency physicians. This facility also has full cardiovascular intervention and intensive care unit (ICU) capacity.

The routine practice for the study EMS is that data on all resuscitations is collected and placed into a custom database for review and follow-up. This practice made available a standardized data source consisting of outcomes for the two treatment protocols of interest covering a time period from November 2002 to August 2005. A formal research protocol was created for data extraction from the EMS database. This protocol was granted exclusion of consent by the local institutional review board that supervised the study EMS.

Cases were defined as all individuals ≥18 years entered into the study EMS database during the study period were determined to be in pulseless cardiac arrest by the paramedic attending the case. Cases were assigned to the epinephrine only or vasopressin plus epinephrine protocols in accordance with the protocol in use at the time they entered the system. Individuals with return of spontaneous circulation (ROSC) after electrical therapy only, were excluded from analysis as were all traumatic cardiac arrests.

The study period spanned a total of 34 months. The resuscitative protocols consisted of protocol P1 (epinephrine, 1 mg intravenously every 3 to 5 minutes) during the first 17 months of the study period, and protocol P2 (vasopressin 40 units intravenously given simultaneously with epinephrine, 1 mg, followed by epinephrine, 1 mg every 3 to 5 minutes) during the final 17 months of the study period. In addition, other standard resuscitative measures were applied per protocol based on the recommendations of the American Heart Association (AHA)–Advanced Cardiac Life Support Program.[1] There were no other changes to the resuscitative protocols, except for the two pharmacologic agents between the two cohorts.

Data collection was performed anonymously from the EMS database and entered into a separate study database in Microsoft Office Excel® (Microsoft, Inc., V. 12.0.6017.5000, Redmond, WA). Processing was performed using the Excel statistical add on packet, Analyze-it® (V. 2.05) for continuous and categorical data and Epi-Info® (V. 3.34) for odds ratios with confidence intervals.

Results

There were 204 cases in the resuscitation database that met the criteria for inclusion, 123 (60.3%) males and 81 (39.7%) females. The mean of their respective age was 64.1 years (median = 65 years; range 19–95 years) with the age distribution demonstrated in Figure 1. Of the 204 cases that met the criteria for inclusion, 191 (93.6%) were administered a study protocol while 13 cases (6.4%) did not receive one of the study protocols. These 13 cases were defibrillated only or defibrillated and ventilated, resulting in ROSC and were excluded from further analysis. Of the remaining 191 cases, epinephrine alone (P1) was administered to 85 (44.5%) and vasopressin plus epinephrine (P2) was administered to 106 (55.5%).

Protocol Assignment

Evaluation of protocol assignment demonstrated that there were slightly more females who were given the P1 protocol as compared to females in the P2 protocol group, $p = 0.03$ (95% CI = 0.007–0.053). However, evaluation of outcomes did not demonstrate a difference in outcome based on sex, $p = 0.27$ (95% CI = 0.27–0.33). No difference was noted in protocol assignment based on age, $p = 0.48$ (95% CI = 0.41–0.55).

Outcomes

Younger age was associated with an improved probability of survival to discharge home in both protocols, $p = 0.003$ (95% CI = 0.004–0.010). Outcomes were evaluated for difference between P1 and P2 at the survival intervals of arrival to the emergency department, survival at 24 hours, and survival to discharge home. No difference in survival was noted between protocols at the level of arrival to the emergency department [61/85 (71.7%) in P1 and 68/106 (64.1%) in P2, OR = 1.42 (95% CI = 0.73–2.76) $p = 0.26$; survival at 24 hours 10/85 (11.6%) for P1 and 21/106 (19.8%) for P2, OR 0.54 (95% CI = 0.22–1.30) $p = 0.133$, or survival to discharge home 7/85 (8.23%) for P1 and 5/106 (4.71%) for P2, OR 1.81 (95% CI = 0.49–6.88) $p = 0.319$]. The relative proportion of survival at the three levels in time is presented in Figure 2.

Discussion

Epinephrine has been the standard medication used in the cardiac arrest patient for several decades. Its adrenergic properties are thought to increase coronary and cerebral blood flow leading to increased electrical impulse formation in pulseless electrical activity (PEA) and asystolic arrests.[1] Vasopressin is an endogenous pressor molecule that creates vasoconstriction via specific vasopressin receptors. Vasopressin administration also is thought to cause increased coronary and cerebral perfusion in patients suffering cardiac arrest.[4] Vasopressin has played a prominent role in the AHA's Advance Cardiac Life Support (ACLS) guidelines beginning with the year 2000 revision and continuing in the 2005 revision of continuous ACLS.[1] In both versions, vasopressin is recommended as an alternative to epinephrine, with the suggestion that epinephrine be added (or resumed) after 20 minutes.[1] These AHA guidelines provide considerable flexibility in the design of resuscitation protocols for cardiac arrest. Despite mounting research regarding the use of vasopressin in cardiac arrest cases, conflicting results often are obtained. One question yet to be answered (particularly for rural EMS systems) is whether there is sufficient benefit to justify the additional cost asso-

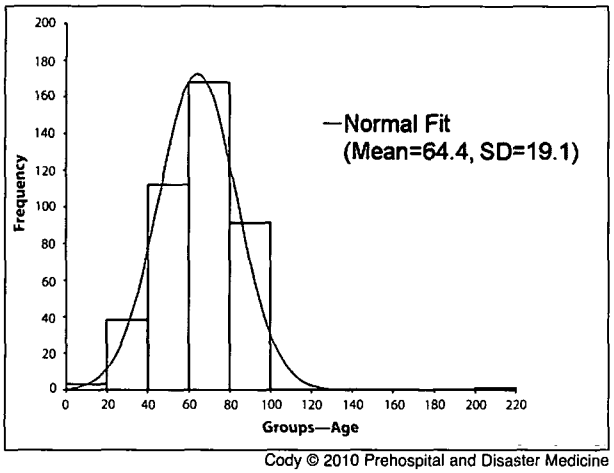

Figure 1—Study population age distribution

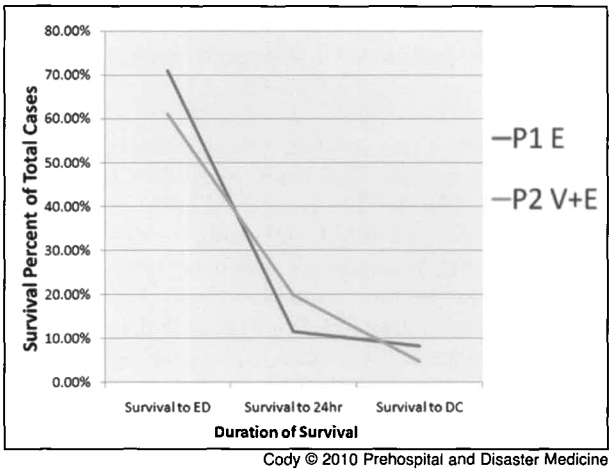

Figure 2—Proportions of survivors from cardiac arrest at three time intervals using P1 (E = epinephrine) and P2 (V + E = vasopressin and epinephrine) resuscitation protocols

ciated with the addition of another drug to the cardiac arrest protocol.

Several studies performed on animal models have compared physiologic effects of epinephrine and vasopressin in induced cardiopulmonary arrest. Prengel and colleagues compared single-dose epinephrine to single dose vasopressin in a porcine cardiopulmonary arrest model and found higher mean aortic blood pressures 15 minutes after resuscitation with vasopressin. They also found higher pulmonary vascular resistance in this group; however, there was no significant difference in respiratory parameters between the two groups.[12] Stadlbauer *et al* compared survival rates in pigs that either received placebo, epinephrine or a combination of epinephrine and vasopressin, at five-minute intervals. This study demonstrated ROSC for all animals treated with the combination of vasopressin and epinephrine, whereas the other study animals perished. Additionally, all of the surviving animals were neurologically normal at five days.[13] Promising results also were reported in a porcine asphyxia model, in which significantly higher coronary perfusion pressures and survival rates were found in animals treated with a combined regimen of epinephrine and vasopressin.[14]

Several porcine studies also have evaluated epinephrine and vasopressin in relation to cerebral perfusion. One study of ventricular fibrillation compared a single dose of epinephrine to a single dose of vasopressin. These results indicated that vasopressin resulted in better cerebral blood flow and less cerebral hypercapnia than epinephrine.[15] Mulligan *et al* determined that when compared to a single dose of vasopressin, the combination of vasopressin and epinephrine induced a higher rate of cerebral blood flow after ROSC. These investigators also noted a more rapid rise in coronary perfusion pressures over a longer time period in animals treated with the combination opposed to either drug alone.[5] However, Wenzel's group reported contrary findings in a porcine model of induced pulseless electrical activity. In this study, cerebral blood flow was significantly higher in pigs treated with vasopressin alone as opposed to the combination.[16] Animal studies are limited by their inherent confounders when attempting to generalize findings to the real world of human resuscitation.

In human trials, the European Vasopressin Study compared outcomes in patients with cardiopulmonary arrest who were treated with either vasopressin or epinephrine. Results from this study indicated that vasopressin was useful particularly in the setting of asystole. In addition, cases treated with vasopressin followed by epinephrine were more likely to survive to hospital discharge than were those treated with epinephrine alone.[17] A Canadian study of in-hospital cardiac arrest cases compared epinephrine and vasopressin as first-line drugs followed by additional doses of epinephrine for patients who failed to respond to either first-line medication. This trial failed to demonstrate a difference between survival rates or levels of neurological outcomes.[6] Gueugniaud *et al* looked at a large cohort of cardiac arrest patients in France in a prospective, randomized, double-blinded design that compared epinephrine alone to a combination of vasopressin and epinephrine given concurrently. The French study varied from the current study in that the vasopressin group received a second dose of vasopressin if return of spontaneous circulation was not achieved within three minutes. There was no benefit in outcomes by adding vasopressin to the cardiac arrest regimen. The authors did note a small but non-significant trend towards improvement in a subset of patients with pulseless electrical activity who received only epinephrine. Not surprisingly, better outcomes were associated with shorter times to CPR, defibrillation, and advanced life support level care. Additionally, many of the patients in this study who survived to admission were subjected to a post-resuscitation hypothermia protocol, which was not in place in the United States at the time of the current study. Finally, inherent differences in the French EMS system, specifically physician staffed ambulances, introduce confounders in the comparison of data.[17] These studies are representative of only a few human studies and demonstrate the often contradictory findings reported with vasopressin in cardiac arrest.

The major weaknesses of this study are the low number of total cases and the retrospective approach of the research

protocol at the survival levels selected. Power estimations were performed that indicated the study did meet adequate numbers of cases to demonstrate a difference between protocols. However, although data were collected regarding neurologic outcomes, insufficient numbers of survivors were obtained to report on this outcome. Other confounders include the fact that the care of prehospital arrest cases occurs in an uncontrolled environment, preventing most efforts to control for variables such as pre-arrival cardiopulmonary resuscitation, EMS response time, the quality of basic life support maneuvers by First Responders, and the time to drug administration.

Efforts to reduce selection bias occurred through the creation and use of a strict protocol and case definition before data abstraction from the study database.[11] One positive aspect of this study is the uniformity of drug regimens during the two protocol time periods that decreases treatment bias.

Conclusions

The combination of epinephrine and vasopressin for atraumatic cardiopulmonary arrest has shown promising but mixed results in many previous trials. This community EMS study using prehospital cardiac arrest cases failed to show an advantage in overall survival with the addition of vasopressin. This study joins the general population of investigations in the scientific literature providing both positive and negative results regarding this topic. It may be that vasopressin provides some advantage in outcomes over epinephrine alone, but that the effect is small enough that many studies are unable to clearly resolve the difference. It is important that further, large-scale investigations be carried out regarding the existence and degree of any impact on survival provided by vasopressin in order to justify the maintenance and use of this agent in the prehospital setting.

References

1. American Heart Association: 2005 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2005;112:IV58–IV66.
2. Hazinski MF, Nadkarni VM, Hickey RW, *et al*: Major changes in the 2005 AHA guidelines for CPR and ECC: Reaching the tipping point for change. *Circulation* 2005;112:IV206–IV211.
3. Wenzel V, Raab H, Dünser MW: Role of arginine vasopressin in the setting of cardiopulmonary resuscitation. *Best Pract Res Clin Anaesthesiol* 2008;22(2):287–297.
4. Zhong J, Dorian P: Epinephrine and vasopressin during cardiopulmonary resuscitation. *Resuscitation* 2005;66(3):263–269.
5. Mulligan KA, McKnite SH, Lindner KH, *et al*: Synergistic effects of vasopressin plus epinephrine during cardiopulmonary resuscitation. *Resuscitation* 1997;35:265–271.
6. Stiell IG, Herbert PC, Wells GA, *et al*: Vasopressin versus epinephrine for inhospital cardiac arrest: A randomized controlled trial. *Lancet* 2001;358:105–109.
7. Lindner KH, Prengel AW, Brinkman A, *et al*: Vasopressin administration in refractory cardiac arrest. *Ann Intern Med* 1996;124:1061–1064.
8. Lindner KH, Dirks B, Strohmenger HU, *et al*: A randomized comparison of epinephrine and vasopressin in patients with out-of-hospital ventricular fibrillation. *Lancet* 1997;349:535–537.
9. Wenzel V, Lindner KH, Augenstein S, *et al*: Vasopressin combined with epinephrine decreases cerebral perfusion compared with vasopressin alone during cardiopulmonary resuscitation in pigs. *Stroke* 1998;29:1462–1468. [Editorial comment].
10. Wayne MA, Racht EM, Aghababian RV, *et al*: Prehospital management of cardiac arrest: How useful are vasopressor and antiarrhythmic drugs? *Prehosp Emerg Care* 2002;6:72–80.
11. Berger V: *Selection Bias and Covariate Imbalances in Randomized Clinical Trials (Statistics in Practice)*. Hoboken: Wiley, 2005.
12. Prengel AW, Lindner KH, Keller A, *et al*: Cardiovascular function during the postresuscitation phase after cardiac arrest in pigs: A comparison of epinephrine versus vasopressin. *Crit Care Med* 1996;24(12):2014–2019.
13. Stadlbauer KH, Wagner-Berger HG, Wenzel V, *et al*: Survival with full neurologic recovery after prolonged cardiopulmonary resuscitation with a combination of vasopressin and epinephrine in pigs. *Anesth Analg* 2003;96:1743–1749.
14. Mayr VD, Wenzel V, Voelckel WG, *et al*: Developing a vasopressor combination in a pig model of adult asphyxial cardiac arrest. *Circulation* 2001;104:1651–1656.
15. Prengel AW, Lindner KH, Keller A: Cerebral oxygenation during cardiopulmonary resuscitation with epinephrine and vasopressin in pigs. *Stroke* 1996;27:1241–1248.
16. Wenzel V, Krismer AC, Amtz HR, *et al*: A comparison of vasopressin and epinepnrine for out-of-hospital cardiopulmonary resuscitation. *N Engl J Med* 2004;350:105–113.
17. Gueugniaud PY, David JS, Chanzey E, *et al*: Vasopressin and epinephrine vs epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med* 2008;359:21–30.