VASOPRESSIN THERAPY DOES NOT IMPROVE RETURN OF SPONTANEOUS CIRCULATION IN OUT-OF-HOSPITAL CARDIAC ARREST

By

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TABLE OF CONTENTS

TABLE OF CONTENTS……..i

LIST OF TABLES……ii

LIST OF FIGURES…….iii

LIST OF ABBREVIATIONS……..……iv

ACKNOWLEDGMENTS……..……..……v

ABSTRACT……vi

BACKGROUND…….1

METHODS……..4

RESULTS……..16

DISCUSSION……20

REFERENCES……..27

LIST OF TABLES

Table 1. Variables used in the analysis.

Table 2a. Verification of 33 randomly selected cases in County 1, abstracted from electronic medical record.

Table 2b. Verification of 30 randomly selected cases in County 2, abstracted from written medical record.

Table 3. Univariate analysis: associations of independent variables with the primary outcome ROSC.

Table 4. Distribution of independent variables amongst treatment groups.

Table 5. Final logistic regression analysis of the association between arrest event characteristics and ROSC.

Table 6. Subgroup analysis of patients presenting with asystole: logistic regression analysis of the association between arrest event characteristics and ROSC.

LIST OF FIGURES

Figure 1. Case selection process for the final analytical data set.

LIST OF ABBREVIATIONS

ACLS	Advanced cardiac life support
AED	Automatic external defibrillator
ALS	Advanced life support
BLS	Basic life support
CI	Confidence interval
CPR	Cardiopulmonary resuscitation
EMS	Emergency medical services
IRB	Institutional review board
NA	Non-applicable
OHSU	Oregon Health & Science University
OPALS	The Ontario Prehospital Advanced Life Support study group
OR	Odds ratio
PEA	Pulseless electrical activity
REF	Reference group
ROSC	Return of spontaneous circulation
SD	Standard deviation
SPSS	Statistical Product and Service Solutions
VF	Ventricular fibrillation
VT	Ventricular tachycardia

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ABSTRACT

Background: Vasopressin increases peripheral vascular resistance and volume retention, without increasing myocardial oxygen demand and ischemia. It therefore has theoretic advantage over epinephrine for the treatment of cardiac arrest. Preliminary animal and human trails supported this theory, however larger randomized trials failed to show an overall benefit. One large human trial suggested that a subgroup of cardiac arrest, those with asystole, uniquely benefited from vasopressin therapy. Our analysis uses data from a large urban EMS system that added vasopressin to standard therapy in the setting of asystole in January 2005. Our study compared the rate of return of spontaneous circulation (ROSC) in patients treated by this EMS system for asystole before and after the protocol change.

Methods: A historical cohort study design was used to determine if the addition of vasopressin to the asystole protocol improved return of spontaneous circulation (ROSC). Two county EMS electronic databases were queried for all patients treated for out-of-hospital asystole from January 2004 through September 2006, one year prior, and one year following the protocol change. Patients were excluded if they suffered traumatic arrest, were younger than 15 years old, or had treatment withheld due to "do not resuscitate" orders. The proportion of ROSC was compared in patients treated before the protocol change (standard treatment) with those treated after the protocol change (vasopressin added treatment). Other variables were collected and according to the Utstein style, and were tested for inclusion in the final model. Logistic regression analysis was used to calculate an adjusted odds ratio.

Results: There was no difference between the two protocol groups in the rate of ROSC [OR = 1.18 (0.72-1.93), standard therapy = ref.). Other secondary independent variables were found to have significant association with ROSC: arrest witnessed by bystander [OR = 2.72 (1.70-4.36)], witnessed by EMS [OR = 4.21 (1.69-10.51)], and time from call to scene greater than 8 minutes [OR = 0.42 (0.21-0.85)].

Conclusion: Our study fails to demonstrate improved return of spontaneous circulation from vasopressin therapy for the treatment of asystole. The study results are consistent with the results of other studies of vasopressin for cardiac arrest.

BACKGROUND

Cardiac arrest is the cessation of cardiac mechanical activity, confirmed by the absence of a detectable pulse, unresponsiveness and apnea.[1] The annual incidence of sudden out-of-hospital cardiac arrest in North America is estimated to be 0.55 per 1,000 population, or approximately 165,000 in the United States annually.[2, 3] Approximately sixty percent of sudden cardiac arrest is treated by emergency medical services (EMS). [4] Survival outcomes from out-of-hospital sudden cardiac arrest vary widely among centers; survival ranges as low as 1%[5] to as high as 15%.[6] A meta-analysis by Nichol reported a median survival to hospital discharge of 6.4%[7].

EMS treatment of cardiac arrest is guided by the Advanced Cardiac Life Support (ACLS), evidence-based guidelines published by the American Heart Association and widely accepted as the standard of care. ACLS guidelines for cardiac arrest include recommendations for bystander response, cardiopulmonary resuscitation technique, procedural interventions such as defibrillation and airway control, and pharmacological therapy.

Pharmacologic therapy is guided by the underlying cardiac arrest rhythm, and may include anti-arrhythmic therapy to promote normal rhythm (e.g., amiodarone and lidocaine), anticholinergic therapy to increase heart rate (atropine), and pressor therapy to improve circulation. Standard pressor therapy for cardiac arrest is epinephrine, which helps promote circulation by increasing peripheral vascular resistance as well as cardiac

output. Epinephrine increases cardiac output by increasing heart rate and contractility, and in doing so increases myocardial oxygen demand and potentially worsens myocardial ischemia**.** Vasopressin increases peripheral vascular resistance and volume retention without increasing myocardial oxygen demand and ischemia, and therefore has a theoretic advantage over epinephrine.[8-15]

Preliminary data suggested that these theoretic advantages would indeed improve outcomes in cardiac arrest. Animal data[8-12] demonstrated improved perfusion of vital organs and better survival in pigs treated with vasopressin during cardiac arrest. A study of ten human subjects, deemed unsalvageable after prolonged arrest, demonstrated that vasopressin but not epinephrine increased cerebral perfusion pressure.[13] A case series reported eight patients who failed standard therapy for cardiac arrest but developed return of circulation following vasopressin therapy.[14] A small prospective randomized trial of forty human subjects by Linder demonstrated marginally significant improvement when comparing vasopressin with epinephrine therapy for out-of-hospital ventricular fibrillation (14/20 vs.7/20 surviving to admission: $p = 0.06$; 12/20 vs. 4/20 surviving 24 hours: $p = 0.02$; 8/20 vs. 3/20 surviving to discharge: $p = 0.16$).[15]

However, two larger randomized human trials published by Stiell in 2001 and Wenzel in 2004 showed no difference in survival in patients treated with vasopressin or epinephrine for cardiac arrest.[16, 17] The Wenzel study, an out-of-hospital randomized trial, demonstrated that a subset of patients, those with asystole, had better outcomes in the vasopressin treated group. More patients with asystole in the vasopressin group were

admitted to the hospital alive [76/262 (29.0) vs. 54/266 (20.3); $p = 0.02$] and more were discharged from the hospital alive [12/257 (4.7) vs. 4/262 (1.5); $p = 0.04$]. [17] While vasopressin did not benefit overall cardiac arrest patients in this study, some interpreted these results as evidence that vasopressin specifically benefits patients with asystole.[18, 19] Critics of this conclusion[20-23]countered that the results are *post hoc* and therefore should not be trusted, and that the cerebral performance outcomes of the additional asystole survivors were dismal. These critics insisted that stronger evidence and further discussion are needed before a wide spread change of practice take place.

The EMS agencies serving the three counties of greater metropolitan Portland participate in a unified protocol development committee with the goal of maintaining similar protocols reached by group consensus. Based on the results of the Wenzel trail[17] the group voted to include vasopressin in the treatment of asystole, but not other types of cardiac arrest. The protocol change took place January 2005 in all three counties: Multnomah, Clackamas, and Washington. This protocol change presented us with a natural experiment to study the effectiveness of our EMS agencies' treatment of asystole before and after the addition of vasopressin to the protocol. This historical cohort study tests the hypothesis generated by Wenzel[17] that vasopressin improves outcomes in asystole.

METHODS

Institutional Review Board Approval:

The Oregon Health and Science University Institutional Review Board reviewed our study protocol and granted approved exempt status (IRB00002905). The protocol was also reviewed and provided by the Research Council of the local emergency medical service provider, American Medical Response.

Study Design:

A historic cohort study design was used to determine if the addition of vasopressin to the asystole protocol improves return of spontaneous circulation.

Location:

The metropolitan area of Portland, Oregon is comprised of three counties served by separate EMS agencies. Two of these counties were chosen for our study because both had similar protocols for asystole in 2004 and underwent a similar protocol change in January 2005. In 2004, both county agencies used standard Advanced Cardiac Life Support (ACLS) therapy for asystole, including pharmaceutical therapy with alternating doses of epinephrine and atropine. Beginning January 2005, both agencies added one 40 unit dose of vasopressin to the existing therapy for asystole. Both county agencies have electronic databases capable of supporting queries and agreed to allow access to the data. Combined data from the two counties were expected to provide an adequate sample size for the study.

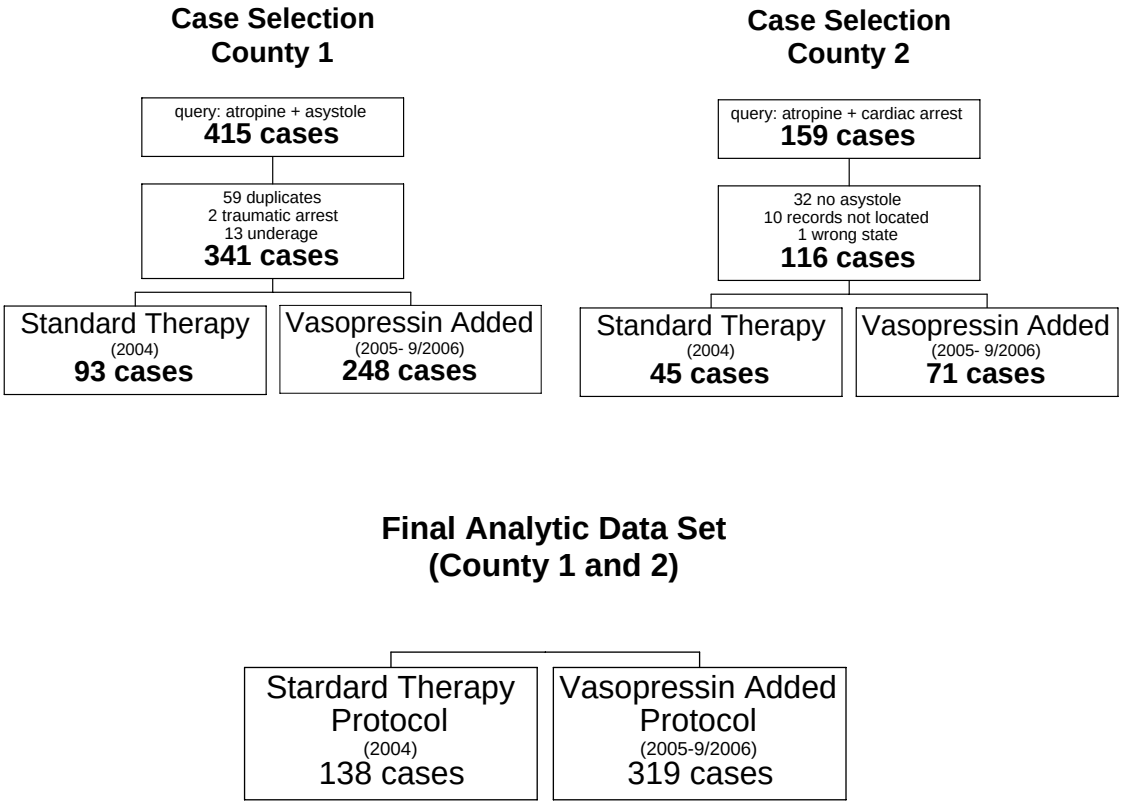
Selection of Cases:

Cases were selected from the two EMS databases by electronic query and review of written medical records. The databases in both counties were queried for cases in the time period of January 2004 through September 2006. Our *a priori* selection criteria included all patients who were treated for asystole at anytime during out-of-hospital ACLS treatment. To enhance the search for treatment of asystole, the databases were also searched for treatment with atropine, a drug used for both asystole and pulseless electrical activity (PEA). Exclusion criteria included patients with suspected traumatic arrest, patients younger than 15 years of age, and those with "do not resuscitate" orders in whom ACLS was withheld (Figure 1).

County 1's EMS database was searched for all patients who suffered "asystole" who also received "atropine". The initial query found 415 records, of which 59 were deleted due to duplication, two (2) were removed because the arrest was due to trauma, and 13 were removed because the patients were younger than fifteen years old. The remaining 341 records were selected for further consideration for entry into the analysis data set. County 2's EMS database did not allow queries specifically for "asystole". Therefore it was searched for any patient who suffered "cardiac arrest" who also received "atropine". The initial query found 159 patients, of which 32 were excluded because they received atropine for PEA, but asystole was not reported. Ten (10) patients were excluded because the record could not be located (5 from each treatment group), and one (1) was

excluded because the arrest occurred outside of the study area. A total of 116 records were available for statistical analysis from County 2.

Figure 1. Case selection process for the final analytic data set.



Variables: The effectiveness of vasopressin added to epinephrine therapy was compared to therapy with epinephrine alone by measuring resuscitation success before and after the protocol change. The primary outcome variable to measure resuscitation success was return of spontaneous circulation (ROSC), reported at any time after treatment was initiated. ROSC was considered to occur in any patient who had a return of a palpable pulse, audible heart sounds or a blood pressure reported by a paramedic in the medical record.

The primary independent variable was based on *protocol change*, not treatment received. Our study compared those treated for asystole prior to the January 2005 protocol change (Standard Protocol) with those treated after the protocol change (Vasopressin Added Protocol). Subjects were included in the Vasopressin Added group even if vasopressin was not actually given. This design helps insure that the two groups have otherwise similar characteristics, reducing the opportunity for selection bias.

Other independent variables were selected from the available data according to the Utstein style[1] guidelines for uniform reporting of data from out-of-hospital cardiac arrest and based on previously published cardiac arrest research.[16, 17, 24-39] These variables included age, gender, county, location (home, public, health care facility), witnessed arrest (arrest unwitnessed, witnessed by a bystander, or witnessed by an EMS agency), bystander cardiopulmonary resuscitation (bystander CPR), first agency on scene (basic life support , advanced life support fire, or advanced life support EMS), time to call, drug route, presenting rhythm (asystole, PEA, ventricular fibrillation (VF) , ventricular

tachycardia (VT), organized), and primary impression. Time to call was collected as continuous data but then was converted into a categorical variable (< 4 minutes, 4-8 minutes, 8+ minutes) to reflect a non-linear trend (Table 1).

Table 1. Variables used in the analysis.

Variable	Type of data	Description
ROSC *(primary dependent variable)*	Nominal	Y/N: return of palpable pulse, audible heart sounds, or blood pressure reported by the paramedic
Protocol change *(primary independent variable)*	Nominal	Prior to protocol change (Standard Protocol, Jan. 1- Dec. 31, 2004) After protocol change (Vasopressin Added Protocol, Jan. 15, 2005- July 31, 2006)
Age (years)	Continuous	15 years of age or greater
Gender	Nominal	Male, female
County	Nominal	County 1, County 2
Location	Nominal	Home, public, health care facility
Arrest witnessed	Nominal	Unwitnessed, bystander witnessed, EMS witnessed
Bystander CPR	Nominal	Y/N
First agency on scene	Nominal	BLS, ALS Fire, ALS EMS
Time from call to scene	Ordinal	<4 minutes, 4-8 minutes, 8+ minutes
Drug route	Nominal	Intravenous, intraosseous, endotracheal
Presenting rhythm	Nominal	First document rhythm: Asystole, PEA, ventricular fibrillation/pulseless ventricular tachycardia, organized rhythm
Primary impression	Nominal	Paramedic documented cause of arrest: cardiovascular arrest, respiratory, toxicological/overdose/environmental

Missing Data:

County 1: Data were obtained by electronic query and was largely complete; however variables *location, first agency on scene, and drug route* contained too many missing data to be used for analysis and were unable to be accurately abstracted from the original records. The primary outcome variable, *ROSC,* was not identified by the electronic query in 64 cases. All 64 were identified by direct review of the electronic medical record. Likewise other variables of interest had occasional missing values that were successfully identified by direct review of the electronic medical record. All variables of interest were therefore complete in each of the 341 cases.

County 2: Data were obtained by direct review of the written medical record by the Principal Investigator. All variables of interest were identified in each of the 116 cases.

Quality Control:

County 1: The Principal Investigator reviewed a random sample of 33 patient records to test the reliability of the electronic database query. The investigator was blinded to the results of the electronic query. Variables essential to the analysis were reviewed, including *protocol change, ROSC, bystander CPR, presenting rhythm, witnessed arrest,* and *time from call to scene.* All of the variables considered demonstrated high agreement, generally well over 90% (Table 2a).

County 2: All variables of interest were obtained by direct review of the written patient record by the Principal Investigator. An independent reviewer was blinded to the results of the initial data collection and given explicit decision rules developed during the initial data collection on how to abstract data from the written chart. A random sample of 30

patient records demonstrated high agreement between the Principal Investigator and the independent reviewer (Table 2b).

Table 2a. Verification of 33 randomly selected cases in County 1, abstracted from electronic medical record.

Variable	Electronic Chart Review	Percentage Agreement	Kappa (95% CI)
Protocol change	33/33	100%	1
ROSC	29/31	93.5%	0.85(0.65-1)
Bystander CPR	32/33	97.0%	0.93(0.79-1)
Presenting rhythm	30/33	90.9%	0.84(0.64-1)
Witnessed Arrest	31/33	93.9%	0.90(0.76-1)
Time from call to scene	33/33	100%	1

Table 2b. Verification of 30 randomly selected cases in County 2, abstracted from written medical record.

Variable	Written Chart Review	Percentage Agreement	Kappa (95% CI)
Protocol change	30/30	100%	1
ROSC	27/30	90%	0.77(0.53-1)
Bystander CPR	29/30	97%	0.91(0.74-1)
Presenting rhythm	28/30	93%	0.88(0.74-1)
Witnessed Arrest	25/30	83%	0.65(0.37-0.93)
Time from call to scene	29/30	97%	0.93(0.81-1)

Final Analytical Data Set:

The data for County 1 and County 2 were combined for a total of 457 cases, 138 in Standard Protocol, and 319 in Vasopressin Added Protocol (Figure 1).

Statistical Analysis:

The data were entered into SPSS (14.0 GP) for analysis. The treatment cohorts, Standard Protocol and Vasopressin Added Protocol, were compared for differences amongst

variables. A Pearson's Chi square test was used for categorical variables and independent two sample *t*-test was used for continuous variables.

All of the independent variables were evaluated for association with the primary outcome, ROSC, through the use of univariate logistic regression. The primary independent variable, variables associated with the primary outcome with *p*-values <= 0.30, and variables with suspected clinical relevance to confounding variables or resuscitation success were considered for the multivariate logistic regression model. All selected candidate variables were entered into a multivariate logistic regression model, and odds ratios were tested for significance. Variables significant at $p < 0.25$ and any other variable suspected of potential interaction were kept in the model to test for interaction. Confounding was also checked in this step.

The main effects model was then tested for interaction. The final model includes the primary independent variable, variables and interactions at a 0.05 level of significance, and important confounding variables. The final model was tested for goodness of fit using the Hosmer and Lemeshow test and diagnostic plots for outliers or influencing points. All reported *p*-values are two-sided, and *p*-values of less than 0.05 are considered to indicate statistical significance.

Statistical Power and Sample Size:

A priori, we calculated statistical power and sample size. The sample size estimate was based on the Chi square statistic comparing proportions of the dichotomous outcome variable, return to spontaneous circulation (ROSC), using an alpha = 0.05 (two-sided) and beta = 0.20. For these calculations, the reference probability of resuscitation (P1) was estimated to be 0.20, and the probability of vasopressin treatment (P2) was estimated to be 0.35 (proportions of subjects in Standard Protocol and Vasopressin Added Protocol groups with return of spontaneous circulation). Sample size was set to be equal in each group and minimum sample sizes of 138 subjects per group were estimated in this crude calculation. To estimate sample sizes required to support statistical analyses that control for potential confounders, an additional calculation was performed. Assuming the R^2 between the primary independent variable and the additional independent variables is 0.09 to 0.15, approximately 160 subjects were estimated to be needed in each group to detect a difference of 0.15 between the two groups.

RESULTS

Characteristics of study population:

EMS response and patient characteristics were distributed similarly amongst protocol change groups, with the exception of county (County 1: 67.4% vs. 77.7%; p=0.02) and gender (male: 70.3% vs. 60.5%; p=0.05). Mean age was 62 years in both groups. There was no statistically significant difference between the groups in the rates of witnessed arrest, bystander CPR, presenting rhythm, primary impression, and time from call to scene (Table 3).

Univariate logistic regression was used to evaluate the association of each independent variable with the primary outcome variable, *ROSC*. The variables associated with *ROSC* at *p*-values < = 0.30, included: *county*, *gender*, *witnessed arrest*, *presenting rhythm*, and *time from call to scene* (Table 4).

Table 3. Distribution of independent variables amongst treatment groups. (Sample size = 457)

Variable	Standard Protocol (N=138)	Vasopressin Added Protocol (N=319)	*p*- value
	Mean (SD) for continuous Frequency (%) for categorical		Independent sample t (continuous) Pearson's chi-Sq (categorical)
County			
1	93(67.4%)	248(77.7%)	0.02
2	45(32.6%)	71(22.3%)	
Age (years)	62.0 (16.4)	62.1 (18.6)	0.98
Gender			
Male	97 (70.3%)	193 (60.5%)	
Female	41 (29.7%)	126 (39.5%)	0.05
Witnessed Arrest			
No	68(49.3%)	175(55.0%)	0.30
Bystander	62(44.9%)	119(37.4%)	
EMS	8(5.8%)	24(7.5%)	
Bystander CPR			
No	95(69.9%)	206(64.8%)	0.30
Yes	41(30.1%)	112(35.2%)	
Presenting Rhythm			
Asystole	89(64.5%)	221(69.3%)	0.11
PEA	21(15.2%)	25(7.8%)	
VF/VT	21(15.2%)	51(16%)	
Organized Rhythm	7(5.1%)	22(6.9%)	
Primary Impression			
Cardiovascular/Arrest	131(94.9%)	297(93.1%)	0.41
Respiratory	5(3.6%)	10(3.1%)	
Tox/Environment	2(1.4%)	12(3.8%)	
Time from call to scene			
<4 minutes	28(21.1%)	49(15.4%)	0.35
4-8 minutes	75(56.4%)	193(60.7%)	
8+minutes	30(22.6%)	76(23.9%)	

Table 4. Univariate Analysis: associations of independent variables with the primary outcome, ROSC. (Sample size = 457)

Variable	No ROSC	ROSC	*p*- value
	Mean (SD) for continuous Frequency (%) for categorical		Independent sample t (continuous) Pearson's chi-Sq (categorical)
Standard Protocol (2004) Vasopressin Added Protocol (2005/06)	103(74.6%) 230(72.1%)	35(25.4%) 89(27.9%)	0.65
County 1 2	 253(74.2%) 80(69.0%)	 88(25.8%) 36(31.0%)	 0.27
Age (years)	62.0(18.1)	62.2(17.6)	0.94
Gender Male Female	 217(74.8%) 116(69.5%)	 73(25.2%) 51(30.5%)	 0.21
Witnessed Arrest No Bystander EMS	 197(81.1%) 116(64.1%) 19(59.4%)	 46(18.9%) 65(35.9%) 13(40.6%)	 0.00
Bystander CPR Yes No	 107(69.9%) 224(74.4%)	 46(30.1%) 77(25.6%)	 0.31
Presenting Rhythm Asystole PEA VF/VT Organized Rhythm	 227(73.2%) 38(82.6%) 51(70.8%) 17(58.6%)	 83(26.8%) 8(17.4%) 21(29.2%) 12(41.4%)	 0.15
Primary Impression Cardiovascular/Arrest Respiratory Tox/OD/Environmental	 310(72.4%) 11(73.3%) 12(85.7%)	 118(27.6%) 4(26.7%) 2(14.3%)	 0.55
Time from call to scene <4 minutes 4-8 minutes 8+ minutes	 52(67.5%) 192(71.6%) 84(79.2%)	 25(32.5%) 76(28.4%) 22(20.8%)	 0.18

Logistic regression model outcomes:

Six independent variables were retained in the final model: *protocol change* was retained as the primary independent variable, and *county, presenting rhythm, witnessed arrest, bystander CPR,* and *time from call to scene*. One interaction term, *bystander CPR x county*, was found to be significant in the final model (Table 5).

The primary independent variable, *protocol change*, was not statistically associated with *ROSC*, indicating that adding vasopressin to standard treatment of asystole had no demonstrable effect (OR = 1.18, 95% CI, 0.72-1.93). Therefore, the null hypothesis was not rejected.

Variables statistically associated with ROSC were *witnessed arrest*, *time from call to scene*, as well as a significant interaction term between *bystander CPR and county*. Compared to unwitnessed arrest, a patient was more likely to experience ROSC if the arrest was either bystander witnessed (OR = 2.72, 95% CI, 1.70-4.36), or EMS witnessed (OR = 4.21, 95% CI = 1.69-10.51). *Time from call to scene* was negatively associated with *ROSC*. Patients with time from call to scene more than 8 minutes were less likely to experience ROSC (OR = 0.42, 95% CI, 0.21-0.85) when compared with patients with time < 4 minutes. The odds of ROSC for the group of time 4-8 minutes, however, was not significantly different from that of time < 4 minutes.

The interaction term *bystander CPR x county* was significant ($p = 0.01$). Bystander CPR was a significant predictor of return of spontaneous circulation in County 1 (OR = 1.92;

95% C.I. 1.12-3.29) and in County 2 was negatively associated but not statistically significant (OR = 0.41, 95% C.I. 0.14-1.24). Additionally, *county* was a significant predictor of ROSC in the absence of bystander CPR (OR = 2.30; 95% C.I. 1.24-4.27), but not when bystander CPR was present (OR = 0.49; 95% C.I. 0.17-1.48).

The Hosmer-Lemeshow goodness-of-fit statistic indicated the final model fit well (p = 0.77) and diagnostic plots did not identify any concerning data points.

A subgroup, those patients presenting with asystole, was analyzed with the logistic regression model, and similar results were produced. The treatment protocol change was again not associated with improved ROSC (OR = 1.35; 95% CI 0.72-2.52). As in the overall model, witnessed arrest, time from call to scene, and the interaction term *bystander CPR x county*, were significantly associated with *ROSC* (Table 6). Results from a model without interaction terms are also provided to show the main effects of *county* and *bystander CPR*. The association between *protocol change* and R*OSC* was very similar to that from the model with interaction (Tables 5 and 6).

Table 5. Final logistic regression analysis of the association between arrest event characteristics and ROSC. (Sample size = 457)

Variable	Model with main effects only		Model including interaction term	
	OR for ROSC (95% CI)	*p*	OR for ROSC (95% CI)	*p*
Protocol change (Standard Therapy = ref.)	1.15 (0.70-1.88)	0.58	1.18 (0.72-1.93)	0.52
Presenting rhythm		0.10		0.09
Organized (ref.)				
Asystole	0.68 (0.28-1.63)	0.38	0.63 (0.26-1.53)	0.31
PEA	0.28 (0.09-0.85)	0.03	0.26 (0.08-0.80)	0.02
VF/VT	0.48 (0.17-1.35)	0.17	0.47 (0.17-1.31)	0.15
Witnessed arrest		0.00		0.00
Unwitnessed (ref.)				
Bystander witnessed	2.75 (1.73-4.40)	0.00	2.72 (1.70-4.36)	0.00
EMS witnessed	4.03 (1.63-9.94)	0.02	4.21 (1.69-10.51)	0.00
Time from call to scene		0.06		0.04
<4 minutes (ref.)				
4-8 minutes	0.81 (0.46-1.44)	0.47	0.79 (0.45-1.42)	0.44
8+ minutes	0.45 (0.22-0.92)	0.03	0.42 (0.21-0.85)	0.02
County (1 = ref.)	1.37 (0.86-2.20)	0.19		
Bystander CPR (no = ref.)	1.54 (0.90-2.64)	0.11		
Bystander CPR x County				0.01
Bystander CPR (no=ref.)				
County 1			1.92(1.12-3.29)	0.02
County 2	NA		0.41(0.14-1.24)	0.12
County (1 = ref.)				
Bystander CPR, N			2.30(1.24-4.27)	0.01
Bystander CPR, Y			0.49(0.17-1.48)	0.21

Table 6. Subgroup analysis of patients presenting with asystole: logistic regression analysis of the association between arrest event characteristics and ROSC. (Sample size = 310)

Variable	Model with main effects only		Model including interaction term	
	OR for ROSC (95% CI)	*p*	OR for ROSC (95% CI)	*p*
Protocol change (Standard Therapy = ref.)	1.34 (0.72-2.49)	0.35	1.35(0.72-2.52)	0.35
Witnessed arrest		0.00		0.00
Unwitnessed (ref.)				
Bystander witnessed	3.23 (1.85-5.66)	0.00	3.21(1.84-5.62)	0.00
EMS witnessed	7.00 (1.78-27.58)	0.01	7.11(1.79-28.14)	0.01
Time from call to scene		0.02		0.02
<4 minutes (ref.)				
4-8 minutes	0.60 (0.29-1.24)	0.17	0.60(0.29-1.23)	0.16
8+ minutes	0.27 (0.11-0.69)	0.01	0.27(0.10-0.67)	0.01
County (1 = ref.)	1.89 (0.96-3.74)	0.07		
Bystander CPR (no = ref.)	1.78 (1.01-3.15)	0.05		
Bystander CPR x County				
Bystander CPR (no=ref.)				
County 1			0.52(0.28-0.96)	0.04
County 2	NA		0.89(0.21-3.78)	0.88
County (1 = ref.)				
Bystander CPR, N			2.18(0.99-4.82)	0.05
Bystander CPR, Y			1.26(0.33-4.90)	0.74

DISCUSSION

We compared the effectiveness of a protocol change adding vasopressin therapy to standard treatment of out-of-hospital asystole by EMS responders. Our historical cohort study failed to demonstrate that the addition of vasopressin to the asystole protocol improves the return of spontaneous circulation. Our results are consistent with results of a randomized in-hospital trial by Stiell[16], and three randomized out-of-hospital trials by Wenzel[17], Callaway[37], and most recently Gueugniaud[40] comparing vasopressin with epinephrine therapy for cardiac arrest. Our data lend further support to the findings of these previous studies by testing the effectiveness of a vasopressin protocol for asystole in two urban EMS systems.

Wenzel failed to show increased return of spontaneous circulation, survival to hospital admission, or survival to hospital discharge in overall cardiac arrest, however reported that the subgroup of patients presenting with asystole experienced significantly improved survival to hospital admission and survival to discharge.[17] As in our study, the asystole subgroup did not demonstrate improved return of spontaneous circulation.[17] Our analysis did not test survival outcome measures.

We believe that out-of-hospital return of spontaneous circulation predicts hospital and discharge survival, and we lack a biologically plausible explanation why Wenzel study patients presenting with asystole and receiving vasopressin had improved survival to hospital discharge, but not improved ROSC.[17] Our results did not demonstrate an

improvement in ROSC and therefore increase our suspicion that the improved survival observed in Wenzel's asystole subgroup occurred by chance.

The Callaway[37] trail compared the usefulness of adding vasopressin to standard epinephrine therapy during out-of-hospital cardiac arrest and failed to show improved return of spontaneous circulation, survival to hospital, or survival to discharge. The study failed to show any difference when adjusted for other variables, or on subgroup analysis, including patients with asystole.

The Gueugniaud[40] trial compared the usefulness of adding vasopressin therapy to epinephrine versus epinephrine alone in out-of-hospital cardiac arrest. The addition of vasopressin failed to show improved return of spontaneous circulation, survival to admission, survival to discharge, 1-year survival, or good neurologic recovery at discharge. Likewise no subgroup, including patients presenting with asystole, benefited from vasopressin therapy.

Additionally a systematic review[41] of vasopressin use in cardiac arrest concluded that vasopressin does not improve outcomes in cardiac arrest, overall or in any subgroup. The investigators suggested that the improved outcomes in asystole demonstrated by Wenzel[17] "may reflect the application of multiple unplanned subgroup analyses, and is not supported by a plausible biological hypothesis."[41]

The independent variables that are associated with ROSC in our study are consistent with those identified in other cardiac arrest research, demonstrating that our study is externally valid. Faster EMS response times predicted better outcome in our study as has previously been demonstrated in EMS studies of cardiac arrest.[26-31] Arrests that were witnessed by a bystander predicted a more favorable outcome in our study, as in previous studies.[29,32] Arrest witnessed by EMS personnel predicted an even more favorable outcome in our study, also demonstrated in previous studies.[33,34] Bystander CPR was associated with improved outcome in our study, also demonstrated in previous studies.[28-31,35,36] The consistency of our findings with those of previous research increases our confidence in the specification of our model using the variables available from the EMS systems.

Power Analysis:

A *post hoc* power analysis estimates the study was adequately powered to detect a 13.7% or larger crude difference in ROSC among the two protocol groups. This represents the observed power and is remarkably close to the *a priori* estimate of a minimum effect size of 15% for 160 subjects recruited into each comparison group. Our logistic regression analysis yielded a point estimate OR of 1.18, a value relatively close to the estimated minimum detectible effect size, however the confidence interval was broad and value of unity is well within the central part of the likelihood distribution of 0.72 to 1.93. The benefit of vasopressin if present is likely to be very small.

Potential Limitations:

We have conducted a novel analysis of the potential benefits of vasopressin in the treatment of out-of-hospital cardiac arrests using data from emergency medical services in a large metropolitan area. Our use of an observational design complements data from several controlled trials, offering an opportunity to develop new data from the applied setting. Several limitations inherent in this design strategy must be recognized.

First, the use of EMS data limited our choice of outcome to ROSC. It was not practical to obtain hospital medical records to consider more distal endpoints such as survival to hospital admission and hospital discharge. Despite this limitation, ROSC is a reasonable surrogate measure for survival. In a small percentage of cases, continued resuscitation efforts during transport and at the hospital ED may result in ROSC that would not be documented in EMS records. Although we judge it to be unlikely, it is possible that protocol change in our study cohort does improve survival despite failing to improve the out-of-hospital ROSC, as was demonstrated by the subgroup analysis of asystole in the Wenzel trail.[17]

A second potential limitation involves reduced statistical power due to a lower than expected proportion of asystole cases receiving the vasopressin therapy. Vasopressin was used in only 62% of the subjects qualifying for its use after implementation of the Vasopressin Added Protocol, which increases the chance of a type II error (failing to reject the null hypothesis if vasopressin is actually effective). The reason why so many patients in the Vasopressin Added Protocol group failed to receive vasopressin is

unknown, but is likely due to several factors. Vasopressin may have been omitted for patients whom paramedics felt treatment was futile. In the dynamic and ever changing course of events that comprise a resuscitation effort, asystole may have occurred briefly and changed to another rhythm before vasopressin could be administered, or asystole may have occurred late in the code after treatment algorithms for other arrhythmias had begun. The Vasopressin Added Protocol patients who presented with asystole received vasopressin more often than those presenting with other rhythms, but still not as often as we expected (71% of patients presenting in asystole received vasopressin vs. 43% of patients with another presenting rhythm).

Potential Bias and Confounding:

Multiple factors contribute to ROSC in out-of-hospital cardiac arrest. Our ability to control for these factors in our statistical analysis was limited to those recorded in the electronic EMS database. Fortunately, most variables identified in previous studies were available for our analysis. The independent variables that we considered (e.g., age, gender, witnessed arrest) were evenly distributed amongst the two protocol change groups (Table 3); however important unmeasured differences may be present which could confound results. In fact, several variables of interest (e.g. location, first agency on scene, and drug route) were incompletely available in the database, and therefore could not be included in the multivariate analysis. Unmeasured differences in the treatment groups more likely contributed non-differential (random) error, and therefore would be expected to cause bias toward the null. Similarly, residual confounding

associated with our measured variables, could further reduce our ability to demonstrate a small benefit of vasopressin therapy.

Our design retrospectively compared cohorts over two consecutive time periods, and unmeasured changes in the treatment protocols may have occurred over time. Although few known treatment protocol changes were made during this time, none of which are expected to have influenced the treatment of asystole, it is possible that other unrecognized operational changes may have occurred that potentially could have influenced results. We believe that operational advancements during the study period would most likely have biased the results away from the null hypothesis, leading us to falsely attribute benefits to the use of the vasopressin therapy.

The threat of selection bias is judged to be small, given that the databases were searched using uniform criteria. Quality control checks of a random sample of the EMS database discovered very few misclassified cases. It is possible that database errors occurred due to the misclassification of electronic or written information by the paramedic or by the Principal Investigator. However our comparison of electronic to written medical records did not reveal substantial differences of omission or commission. It is possible that observer bias could have been introduced during the written chart abstraction process because the independent investigator could not be blinded to the date and therefore had knowledge of the year and protocol intent while reviewing medical records. We attempted to minimize this bias to the extent practicable by using strict search criteria during both electronic and written chart abstraction.

Further research:

The results of our historical cohort study are consistent with the results of at least three randomized trials and a meta-analysis showing no overall benefit in resuscitation and survival from cardiac arrest.[16, 17,37,40,41] While our study only involved those patients who experienced asystole during cardiac arrest, no biological explanation is apparent to explain why vasopressin would be more effective for one cardiac arrest rhythm over another. We feel that further research into the effectiveness of vasopressin for asystole is unnecessary. Currently there is little support for vasopressin's use in out-of-hospital cardiac arrest, either for asystole alone, or cardiac arrest overall. If vasopressin does improve outcomes in cardiac arrest, the benefit to patients is likely very small and would be costly to demonstrate in additional randomized trials.

Overall survival from all-cause cardiac arrest in large U.S. cities is estimated to be as low as 1%, and as high as 15%, with a median of 6.4%. [5,6,42,43] Asystole is an especially poor prognostic indicator compared with other presenting rhythms of cardiac arrest.[32, 44] Despite repeated efforts to improve treatment, the dismal outcomes of cardiac arrest, particularly asystole, has prompted some to question the wisdom of continuing to expend health care resources on this condition.[32, 43,45] Others believe that the poor prognosis of cardiac arrest warrants further efforts to improve care, and that even small incremental improvements, when linked together in "the chain of survival," may eventually lead to more acceptable survival rates. [38,46] Indeed, broader training of the public in CPR,

increased public access to automatic external defibrillators (AEDs), and decreased EMS response times have yielded improved outcomes in cardiac arrest.[38, 46] However thus far, scant evidence exists indicating that any pharmacological therapy improves survival in cardiac arrest. The Ontario Prehospital Advanced Life Support (OPALS) study group reported in a large multi-center prospective trial that ACLS cardiac arrest interventions, including pharmacological therapy, when added to early defibrillation, failed to improve survival to hospital discharge.[39]

Based on our study and the weight of evidence from previous research, we cannot recommend vasopressin for the treatment of asystole. Resources should be focused on non-pharmacological interventions with proven benefit for all-cause cardiac arrest.

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