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Outcome of Children Receiving Epinephrine plus Vasopressin vs. Epinephrine alone during In-hospital Cardiac Arrest

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Abstract

Objective: Our objective was to compare the effects of combination of vasopressin and epinephrine with epinephrine alone on rates of return of spontaneous circulation (ROSC) and mortality in children with in-hospital cardiopulmonary arrest (CPA).

Methods: This was a retrospective chart review of children with cardiac arrest admitted to the Pediatric intensive care unit (ICU) of a tertiary care hospital in North India between May and July 2012. The study period was divided into two intervals- period 1 where only epinephrine was used and period 2 where a single dose of vasopressin was used at a dose of 0.8u/kg in addition to epinephrine. Children were resuscitated as per the 2010 AHA guidelines for cardiopulmonary resuscitation (CPR) during both time periods. Data regarding baseline characteristics, clinical course and predetermined clinical outcomeswere recorded in a pre-structured proforma. Data was entered into Microsoft excel and analyzed using *Stata* 11.

Results: A total of 28 case records of children with CPA were retrieved during the study period. Of these only 6 (21%) children survived to hospital discharge while the remaining children (n= 22, 19%) succumbed to their illnesses. A total of 14 children each were enrolled during the two time periods. The most common reasons for ICU admission as well as mortality were severe sepsis and septic shock seen in almost all (n=14) the children in period 1 and 85% (n=12) of the children in period 2. Compared to period 1 children from period 2 were sicker at admission with higher mortality risk scores(p=0.03) higher incidence of tachyarrhythmia and of refractory shock.

Almost 50% (n=7) of the children receiving vasopressin as the second drug had ROSCimmediately after the arrest in comparison to 43% (n=6) of children receiving epinephrine alone. At 24 hours however, only 5(35%) and 4 (28.6%) of these children from period 2 and period 1 respectively were found to be surviving. Ultimately only 2 children (14%) from period 2 and 4 children (28.6) from period 1 survived to hospital discharge. The differences between the two time periods with respect to all of these primary outcomes were statistically insignificant (p>0.05).

Conclusion: Use of vasopressin as an add-on drug during CPR did not seem to affect the clinical outcomes of children with in-hospital cardiac arrest in comparison to the standard practice of using epinephrine alone.

Key words: CPR; Cardiopulmonary resuscitation; Vasopressin; Epinephrine, In-hospital cardiac arrest.

Introduction

Cardiac arrest both in-hospital and out-of-hospital is a significant cause of mortality and morbidity in the pediatric age group. Nearly 40% of cardiac arrests are in-hospital arrest of which only 27% are reported to survive (1, 2). The management of children with cardiac arrest irrespective of the setting is as per the recommendations of the American Heart Association (AHA) guidelines for cardiopulmonary resuscitation and emergency Cardiovascular Care (3). The first step in the management of cardiac arrest after a patient does not respond to basic life support, is to identify the type of rhythm. Shockable rhythms, i.e. ventricular tachycardia/ fibrillation (VT/VF) should be given immediate defibrillation. However, asystole or

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pulseless electrical activity (PEA) as the initial rhythm or persisting VT/VF after 2 shocks require prompt administration of epinephrine (3).

Epinephrine has formed the backbone of these recommendations for many decades, based mainly on the success of this drug in animal models(4-6).Till date, no prospective clinical trial hasclearly demonstrated its efficacy in improving outcomes of cardiac arrest in humans. Thus a search for other potential drugs had become essential. One such drug is vasopressin, high levels of which have been found in successfully resuscitated adults(7,8). It had therefore become the centre of many studiesover the years to determine its efficacy in cardiac arrest.The evidence generated from years of research in adults has resulted in vasopressin being given a class IIb recommendation in adult cardiac life support guidelines. The ACLS guidelines 2010 permits use of a single dose of vasopressin to replace 1st or 2nd dose of epinephrine in pulseless arrest with an 'indeterminate' level of recommendation (9). With regard to Pediatric Advanced cardiac Life Support however, there is no recommendation for or against its use (class indeterminate) in the guidelines owing to a scarcity of literature on the use of this drug.

In pediatric asphyxiated animal models the combination of vasopressin and epinephrine was superior (10) to epinephrine or equal to it (11). In children, vasopressin was first reported to be beneficial in a retrospective case series in 2002 (12) wherein beneficial effects of vasopressin (0.4units/kg/dose) was found in patients with prolonged cardiac arrest not responding to conventional CPR.A recent prospective feasibility pilot study (13) examined the use of vasopressin in in-hospital cardiac arrests in children and found that patients given vasopressin were found to have increased 24 hour survival, though there was no difference in ROSC, survival to hospital discharge, or favorable neurological outcome.

Given this background we decided to compare the effects of vasopressin after the initial 3 doses of epinephrine vs. epinephrine alone on rates of return of spontaneous circulation and mortality.

Materials and Methods

Design and setting

This was a retrospective chart review of children with cardiac arrest admitted to the Pediatric intensive care unit (ICU) of a tertiary care hospital in North India between May and July 2012. The study period was divided into two intervals- period 1 where only epinephrine was used (May and 1st 2 weeks of June) and period 2 where vasopressin was used in addition to epinephrine (last 2 weeks of June andJuly).

Subjects and data collection

The case records of all children d"17 years of age admitted to the PICU during the study periodswho had cardiopulmonary arrest (CPA) requiringchest compressions and/or defibrillation,and had received all three doses of epinephrine were retrieved. Patients were excluded if first-dose epinephrine was given via the endotracheal tube or parents refused to give verbal consent and previous enrollment. After the advent of the 2010 PALS guidelines which does not give any specific recommendation for or against the use of vasopressin in pediatric cardiac arrest, we had attempted to make it a protocol of administering vasopressin in case of failure of return of spontaneous circulationafter the initial three doses of epinephrine. This was done during the period as mentioned above (June –July). Before administering vasopressin to any child we would obtain informed verbal consent from one of the parents of each child while the third dose of epinephrine was being administered. Vasopressin is readily available in our hospital formulary and is routinely being used as a second line agent in septic shock at starting dosage of 0.01u/kg/hr. We observed beneficial effect of this drug in the initial 2-3 patients in whom it was administered in case of arrest and therefore we decided to continue using the drug subsequently (June- July) as mentioned above.

However, before incorporating it into our PICU protocols we decided to evaluate the effects of this combination therapy in comparison to use of epinephrine only on important clinical outcomes such as sustained return of spontaneous circulation and survival.

Objectives and outcome measures

Our primary objectives were to compare the effect of use of combination therapy of epinephrine and vasopressin (period 2) with use of epinephrine only (period 1) in children with in-ICU cardiac arrest on *a)* proportion of children with return of spontaneous circulation (ROSC) immediately after the arrest and *b)* sustained ROSC at 1 hour and 24 hours after arrest. Return of spontaneous circulation is defined as return of heart beat/ palpable carotid pulsations (ROSC) immediately post arrest (15). Sustained return of spontaneous circulation at 1 hour is defined as ROSC sustained at 1 hour after ROSC. Sustained ROSC at 24 hours is defined as ROSC sustained at 24 hours after ROSC. If a child suffered more than one cardiac arrests during his/her hospital stay only the data of the first cardiac arrest was used for the purpose of the study and the same drug regimen was followed throughout his/her hospital stay.

The secondary objectives were to compare the effects of these two treatments on proportion of children requiring prolonged CPR, duration of CPR, duration of sustained ROSC in those who died, survival to hospital discharge and neurologic outcomes as measured by change in pediatric cerebral performance category (PCPC) scores (14) from baseline. Proportion of children requiring prolonged CPR is defined as 'no of patients requiring prolonged CPR (>20 minutes) to achieve sustained ROSC' (15). Duration of CPR is defined as the interval between the beginning of CPR and the return of spontaneous circulation.Twenty four hour survival is defined as number of patients surviving at 24 hours and survival to hospital discharge is defined as discharge from the hospital either to home or to another facility in a stable condition.

Survival to hospital dischargewas defined as neurologic outcome as per the PCPC scale the components of which are *1)* normal age-appropriateneurodevelopmental function, *2)* milddisability, *3)* moderate disability, *4)* severe disability,*5)* coma or vegetative state, and *6)*brain death. The method of scoring the PCPC scale is provided in panel 1. Favorable neurologic outcome at hospital dischargewas defined as a PCPC of 1–3 or PCPCunchanged from hospital admission.We also recorded the adverseevents following AVP administration such as proportion of children developing thrombocytopenia (platelet count <100000) after resuscitation, proportion with increased liver transaminases, hyponatremia, acute kidney injury (AKI), allergic reaction, hypertension (immediately after the dose), and/or theneed for dialysis (13).

Study methods

Children with CPA were resuscitated according to the 2010 AHA-PALS guidelines (3). Accordingly,as soon as a child was found to be in CPA chest compressions were initiated followed by support for breathing if the patient was not on a ventilator or if the patient was already on a ventilator both chest compressions and ventilations were delivered simultaneously. Subsequently cardiac rhythm evaluation was done and defibrillation performed if indicated. Adrenaline was administered as the first vasopressor in all cases at a dose of 0.01mg/kg intravenously. In cases of asystole or ventricular tachycardia/ fibrillation not responding to CPR including the initial 3 doses of ADR and/or shock vasopressin was given as the second vasopressor at a dose of 0.8 U/kg(13) during period 2 as previously mentioned. If furtherdoses of medication were required, epinephrinewas administered as per the pediatricadvanced life support guidelines until theend of the event. Only patients with in-ICU arrests were included and not those presenting in cardiac arrest to the ICU or those developing arrest in the ward after being shifted out. Although we cannot be assertive about the quality of CPR performed by the physicians and nurses we are certain that good

Panel 1. Pediatric Cerebral Performance Category score

Score 1. Normal - Normal; at age-appropriate level; school-age child attending regular school classroom

Score 2. Mild disability - Conscious, alert, and able to interact at age-appropriate level; school-age child attending regular school classroom, but grade perhaps not appropriate for age; possibility of mild neurologic deficit

Score 3. Moderate disability - Conscious; sufficient cerebral function for age-appropriate independent activities of daily life; schoolage child attending special education classroom and/or learning deficit present

Score 4. Severe disability - Conscious; dependent on others for daily support because of impaired brain function

Score 5. Coma or vegetative state- Any degree of coma without the presence of all brain death criteria; unaware, even if awake in appearance, without interaction with environment; cerebral unresponsiveness and no evidence of cortex function (not aroused by verbal stimuli); possibility of some reflexive response, spontaneous eye-opening, and sleep-wake cycles

Score 6. Brain death Apnea- areflexia, and/or electroencephalographic silence

quality CPR was delivered by all our team members at any point of time. In a previous study from our institute (16) we observed that there was a decline in resuscitation knowledge and skills with time among the nursing staff posted in the ICU and therefore we had made it a unit policy to update/retrain the nurses and residents at 3 monthly intervals and evaluate them appropriately every 3 months using laederal skill meter for ensuring delivery of good quality CPR (which included appropriate rate and depth of ventilation, adequate rate and depth of chest compressions and minimal interruptions in between CPR) to the sick children at all times.Therefore we presumed that the quality of CPR performed to be optimal during the study period. We collected data regarding baseline characteristics such as age, gender, admission diagnosis, cause of cardiac arrest, admission pediatric index of mortality (PIM) scores, pediatric logistic organ dysfunction score (PELOD), clinical course including need for mechanical ventilation, need for inotropes, need for blood products and dialysis. We also collected information regarding the outcome variables such as return of spontaneous circulation, sustained return of spontaneous circulation and critical outcome such as death or discharge from the hospital and PCPC scores at discharge in case of survival to hospital discharge.

Statistical analysis

Data were analyzed using Stata 11.2 (StataCorp, College Station, TX). Categorical data are presented as number (%) while continuous variables are presented as mean (SD), if normally distributed and median (interquartile range), if skewed. Statistical analysis was performed using Student's t-test, Wilcoxon rank sum test and Chi-square test for continuous and categorical variables respectively. A p-value of 0.05 was considered significant.

Results

A total of 112 children were admitted during the 3 months. Of these 28 children had suffered one or more episodes of cardiac arrest and 22 succumbed (19%). Only 6 (21%) children survived to hospital discharge. Of the 28 children 14 children each were enrolled from the two time periods.The baseline characteristics of the studied children during the two time periods are described in table 1. When we compared the baseline characteristics of the two groups we found that females were in majority during both periods. The most common reason for ICU admission was sepsis/ severe sepsis (n=14 vs. n=12, p=0.24) during both periods with the focus of infection being the lung commonly(n= 8, 57%) in period 1 as compared to period 2

(n=4, 29%). Children receiving epinephrine plus vasopressin had higher PIM and PELOD scores in comparison to children receiving epinephrine only, the difference being statistically significant for PIM scores only (p=0.03). The common causes of death in those admitted were refractory shock and hypoxemia during both periods and raised ICP in addition in period 1.

The predominant arrest rhythm in both groups was asystole with only 1 child in period 1 (VF) and 3 children in period 2 (2 had VF and 1 had VT) having tachyarrhythmia's. The average number of doses of epinephrine required was almost similar at both time pointswith the maximum number of doses in period 1 being as high as 9 in few cases. The average duration between cardiac arrest and termination of resuscitation efforts was 20 minutes at both time points in those dying.

Primary outcomes

Almost 50% (n= 7) of the children receiving vasopressin as the second drug had return of spontaneous circulation immediately after the arrest. In comparison nearly 43% (n=6) of children receiving epinephrine only had ROSC. However, 1 hour after revival 43% (n=6) of children fromboth time periods continued to have spontaneous circulation, the difference between the two groups being statistically insignificant (p=0.7). At 24 hours the proportion of children with sustained

Table 1: Baseline characteristics of children from the two time periods

Variables	Period 1 (Epinephrine alone) N=14	Period 2 (Epinephrine + Vasopressin) N=14	P value
Median age (years)	8 (1, 14)	3 (0.2, 11)	0.02
Female gender	8 (57)	9 (64)	1
Diagnostic subgroups (admission)			0.4
Sepsis/severe sepsis	14 (100)	12 (85)	
○ CNS infection	2 (14)	0	
○ GIinfection	2 (14)	0	
○ Respiratory infection	8 (57)	4 (29)	
○ Urosepsis	0	2 (14)	
○ Skin and soft tissue	2 (14)	2 (14)	
○ Without focus	0	4 (28)	
Poisoning	0	0	
Liver failure	0	0	
Congestive heart failure	0	2 (14)	
Any underlying chronic illness			0.2
CKD	1 (7)	0	
CHD	0	2 (14)	
PIM score	-2.2 (-1.6)	-2.9 (2)	**0.03**
PELOD score	10.7 (5.2)	15.5 (6.3)	0.3
Cause of arrest			0.05
Refractory shock	6 (42)	11 (78)	
Refractory hypoxemia	4 (28)	2 (14)	
Raised ICP	4 (28)	0	
Refractory CHF	0	1 (7)	
Resuscitation details			
Tachyarrhythmia	1 (7)	3 (21)	0.73
Asystole	13(92)	11 (78)	-
Epinephrine no. of doses	2.5 (1, 7)	3 (3,5)	0.43
Duration between CA and death (min)	30 (20, 30)	30 (22, 85)	0.29
Hospital course			
Need for mechanical ventilation	14 (100)	14 (100)	undefined
Need for inotropes before arrest	8 (57)	12 (85)	0.12
Median duration -inotropes before arrest (hrs)	8 (5, 48)	20 (8, 38)	0.38
Median duration of ICU stay (days)	1.3 (0.4, 2.5)	3.5 (0.5, 12)	0.38

CNS, central nervous system; GI, gastrointestinal; CKD, chronic kidney disease; CHD, congenital heart disease; PIM score, Pediatric index of mortality score; PELOD score, Pediatric logistic organ dysfunction score; ICP, intracranial pressure; CHF, congestive heart failure; ICU, intensive care unit

Table 2: Primary and secondary outcomes of the study population

Variables	Period 2 (Epinephrine + Vasopressin) N=14	Period 1 (Epinephrine alone) N=14	Adjusted OR (95% CI)	P value
Primary outcomes				
ROSC	7 (50)	6 (42.8)	1.16 (0.52, 2.5)	0.7
Sustained ROSC at 1 hour	6 (42.8)	6 (42.8)	1 (0.42, 2.3)	1.0
Sustained ROSC at 24 hours	5 (35.7)	4 (28.6)	1.25 (0.42, 3.7)	1.0
Secondary outcomes				
Need for prolonged CPR	7 (50)	7 (50)	1 (0.47, 2.1)	1.00
Duration of CPR	20 (12, 30)	20 (6, 30)	-	0.94
Survival to hospital discharge	2 (14.3)	4 (28.6)	0.5 (0.1, 2.3)	0.64
Duration of sustained ROSC (hrs.) – in those who died	30 (30, 40)	30 (20, 76)	-	0.91
Change in PCPC scores	-1.25 (0.95)	-1.5 (0.7)	0.25 (-1.9, 2.4)	0.76

spontaneous circulation declined further at both time points (table 2).

Secondary outcomes

When we compared the secondary outcomes between the two time periods we found that the proportion of children requiring prolonged CPR (>20 minutes) or being discharged from the hospital was comparable between the groups (table 2) although the numbers were higher in the epinephrine only group. The median duration of resuscitation did not differ between the groups and was 20 minutes on an average in both (table 2). However the duration of ROSC was insignificantly prolonged in children receiving vasopressin in addition to epinephrine in comparison to those receiving epinephrine only (table 2). There was no significant difference with regard to other secondary outcomes, such as,change in PCPC scores from baseline to discharge among those surviving to hospital discharge between both groups (Table 2).

Discussion

In this retrospective study of 22 children with in-hospital cardiac arrest we observednosurvival benefit with vasopressin as an add-on drug in cardiopulmonary resuscitation in comparison to the standard practice of using epinephrine alone. However, there was an insignificant trend towards increased proportion of children with ROSC and sustained ROSC at 24 hours (24 hour survival) in those receiving vasopressinin addition to epinephrine when compared to use of epinephrine alone. Unfortunately, this did not translate into survival benefit or benefit in terms of improved neurological outcome in such patients. Our study findings are therefore in accordance with few of the previously reported studieswhich showed neutral results meaning, results not favoring one drug over the other (17-19). However,as discussed earlier, there was an insignificant trend towards improved ROSC and 24 hour survival in our study similar to many of the prior studies in the adult population (20-23). The small numbers evaluated in our study probably resulted in this lack of significant effect seen in our study population.

In addition, there could have been several other explanations as to why our study population responded poorly to use of vasopressin epinephrine combination in comparison to epinephrine alone. Important among these could be *a)* higher PIM scores in children admitted during period 2 which could have made this group more vulnerable *b)* greater proportion of childrenwith refractory septic shock in the same group c*)* increased proportion of children with VF/VT in this

group and finally *d)* only a single dose of vasopressin was administered after the 3rd dose of epinephrine which could have been a suboptimal dosage or inappropriate timing for the drug to show any favorable response.

We observed that children with VF/VT as the initial rhythm did not respond favorably to vasopressin in our study population similar to previous studies in adults. These findings are in contrast to the expected physiologic effects of this drug observed in animal models with ventricular fibrillation. When compared with epinephrine under laboratory conditions in animals with ventricular fibrillation, it was found to have several benefits. It improved coronary systolic and diastolic perfusion pressures, generated higher left ventricular myocardial flow, and produced a higher coronary venous pH (24- 26). This effect on coronary perfusion pressure occurred after every dose of vasopressin as compared to a one time effect with only the first dose of epinephrine. Not only did it improve cardiac perfusion but also improved cerebral blood flow. Furthermore, the effects of vasopressin on vital organs lasted longer than epinephrine and it was also more effective in resuscitating swine models with prolonged cardiac arrest without causing any significant neurological deficit (24-26). From the above discussion it is clear that vasopressin is beneficial in animal models with ventricular fibrillation. However, in human beings why the reverse phenomenon is observed with vasopressin is not clear. A probable assumption could be that in cases of prolonged asystolewith out of hospital or in-hospital cardiac arrest, a state of epinephrine resistance from down-regulation of catecholamine receptors may occur which makes these patients less responsive to epinephrine. As vasopressin acts via different receptors it may have a favorable response in this population.

Vasopressin is known to act Via V1 receptors in vascular smooth muscle cells and cause peripheral vasoconstriction unlike other vasopressors which act predominantly by their action on alpha or beta receptors (23, 24, 26). Therefore, in cases of refractory septic shock where there is receptor down regulation, vasopressin should have had beneficial effect in such cases as compared to epinephrine as most patients would already be on epinephrine at the time of arrest. However we observed that patients with refractory septic shock did not respond favorably to vasopressin. It is well known that refractory septic shock has a mortality rate of almost 50% (28) despite best efforts due to factors such as organ dysfunction, coagulopathy and acidosis. Such patients are unlikely to respond to a single large dose of vasopressin in cardiac arrest as they may succumb to complications of the disease as such- like bleeding, acidosis and associated myocardial dysfunction which would make them unresponsive to any kind of resuscitative efforts.

We also observed that prolonged duration of cardiac arrest did not respond favorably to the administration of vasopressin in our study population contrary to what has been reported in adults (21, 27). This could probablybe attributed to *1)*differences in the cause of arrest which is most often respiratory in origin in children (29) in contrast to adults where it is of cardiac origin and *2)*differences in the physiologic response to disease states between these two patient populations.

The strength of our study is that the findings of our study would certainly add to the scant literature on vasopressin in pediatric cardiac arrest as there are large knowledge gaps in this subject with only few observational studies and a recent feasibility pilot trial as discussed earlier. The major limitations of our study are the inadequate sample size and retrospective nature. A large randomized controlled trial with an adequate sample size may provide definitive answers to the hypothesis generated from our study. The other limitation is that we used vasopressin only after 3rd dose of epinephrine and did not evaluate the effect of vasopressin replacing the second or third dose of epinephrine. Also, we had not evaluated the effect of this combination in children with out of hospital cardiac arrest which accounts for a significant

proportion of cardiac arrests in the community.

In conclusion, use of vasopressin did not seem to affect the clinical outcomes of children with in-hospital cardiac arrest in comparison to epinephrine alone. However, our study findings need further validation through adequately powered clinical trials in both in-hospital and out of hospital cardiac arrest settings, before anyrecommendations could be made about the use of this drug in pediatric CPR.

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