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Management of Pediatric Emergencies: Current Evidence from Cochrane/ other Systematic Reviews

Clinical Question: Is Vasopressin Beneficial in Pediatric Cardiac Arrest?

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Abstract

Epinephrine is the recommended agent for the medical treatment of all forms of cardiac arrest according to the European Resuscitation Council and American Heart Association guidelines. The same guidelines also permit the use of vasopressin as an alternate to epinephrine in cardiac arrest. In this issue we have tried to focus on the literature available on the use of vasopressin in cardiac arrest, and its advantages, if any, when used in lieu of or simultaneously with epinephrine.

Keywords: Cardiac arrest, epinephrine, vasopressin, return of spontaneous circulation.

Introduction

An 18 month old child in the emergency department becomes unresponsive. The child appears pale with slow respiration. Assisted ventilation with a bag and mask device using 100% oxygen is begun. On primary assessment, no heart sounds are audible and central and peripheral pulses are absent. Cardiac monitor shows asystole. Immediately CPR is begun with chest compressions and bag and mask ventilation in the ratio of 30:2. IV epinephrine is also given at 0.01mg/kg (1:10,000: 0.1ml/kg). CPR is continued but there is no return of cardiac activity. Three successive doses of epinephrine are given according to the PALS guidelines but child continues to be in asystole.

The child continues to be in cardiac arrest despite optimal resuscitation measures. The questions that come to your mind at this point would be:

1. Is there any other drug which can be used after 3 doses of epinephrine fail to restore circulation in an infant/child with cardiac arrest?

2. If yes, is vasopressin one such drug?

3. Is vasopressin more beneficial if given earlier in the resuscitation protocol?

4. Are there any guidelines available for the use of vasopressin in cardiac arrest?

Clinical question

Is vasopressin beneficial in cardiac arrest? If yes, should it be used along with epinephrine or after 3 doses of epinephrine?

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, persisting VT/VF after 2 shocks, and initial asystole or pulseless electrical activity (PEA) require prompt administration of epinephrine. In 2000, the International Liaison Committee on Resuscitation (ILCOR) and the American heart Association (AHA) added vasopressin in the Advanced Cardiac Life Support (ACLS) algorithm for VF [1]. It was given a class IIb recommendation defined as 'safe, acceptable, clinically useful, and considered optional or

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alternate treatment'. This recommendation was based on supporting animal studies and preliminary clinical data [2] demonstrating positive results with vasopressin in refractory VF. However, subsequent trials did not show significantly positive results. In 2005, ACLS permitted a single dose of vasopressin to replace 1st or 2nd dose of epinephrine in pulseless arrest with an 'indeterminate' level of recommendation [3]. In 2010 the same recommendation was given a class IIb recommendation [4]. With regard to Pediatric Advanced cardiac Life Support, there was no recommendation for or against its use (class indeterminate) in both the guidelines.

Use of Vasopressin in Cardiac Arrest

Evidence from Cochrane and other systematic reviews

Till date, there is no Cochrane review available on this topic. Numerous meta-analyses have disregarded any benefit with vasopressin use in cardiac arrest. However, they had included studies with diverse methodologies and thus may not be so systematic [5-8]. One meta-analysis reported a clear advantage with vasopressin use in animals but not in humans [9]. Only a single systematic review reported a better ROSC with the combination of both drugs [10].

Evidence in children

Till date, there is no randomized controlled trial (RCT) in children regarding the use of vasopressin in cardiac arrest. However, a recent prospective feasibility pilot study [11] examined the use of vasopressin in in-hospital cardiac arrests in children. Their objective was to assess the feasibility of a large, randomized controlled trial of combination epinephrine- vasopressin for in-pediatric intensive care unit cardiopulmonary arrest refractory to initial epinephrine dosing.

Methodology

All patients <18 yrs of age with cardiac arrest requiring chest compressions with epinephrine were included (n=10). Patients who remained in arrest despite an initial dose of epinephrine received vasopressin (0.8 U/kg) rescue as the second vasopressor, followed by additional epinephrine if needed. Data were compared to a retrospective, matched cohort of patients who experienced cardiopulmonary arrest requiring > two doses of vasopressor, and did not receive vasopressin (n=20).

Results

There was increased 24-hr survival (80% vs. 30%, OR: 9.33, 95% CI: 1.51–57.65) in vasopressin patients. There was no significant difference in return of spontaneous circulation (ROSC), survival to hospital discharge, or favorable neurologic status at discharge.

Conclusions

The authors concluded that their pilot study paved the way for a larger randomized controlled trial of arginine vasopressin therapy during cardiopulmonary resuscitation for in-hospital pediatric cardiac arrest.

Other pediatric studies

The largest study till date on the use of vasopressin in pediatric cardiac arrests was a survey published in 2005 [12], which was done to assess the landscape of vasopressin use and its benefits over epinephrine. Out of the total 1293 patients included, only 5% had been given vasopressin. These patients had longer arrest duration compared to those who did not receive vasopressin, which may be a possible reason why these patients had worse ROSC. Nevertheless, there was no difference at 24 hours or discharge survival.

Adult studies

There are several adult studies comparing the efficacy of vasopressin to epinephrine in out-of-hospital and in-hospital cardiac arrests (OOHCA, IHCA). Most of these studies used vasopressin (initially either one or two doses according to ACLS guidelines) followed by 'rescue' therapy with epinephrine if required [13-17]. Others compared combination vasopressin-epinephrine doses to epinephrine alone [13-17]. There is only 1 study comparing vasopressin solely to epinephrine [18]. Results have been variable. Higher ROSC rates have been reported several times with the use of vasopressin [13, 16, 17, 19] but most studies reported no difference in 24 hour survival, survival to admission or discharge, or neurological outcome.

Clinical Question

Is Vasopressin Beneficial in Pediatric Cardiac Arrest?

Table 1: Summary of studies comparing vasopressin and epinephrine in adults

	Year	N	In or out of Hospital cardiac arrest	Results	Conclusion with respect to Vasopressin
Lindner et al [13]	1997	40	OOHCA	Higher ROSC and 24 hour survival with vasopressin without rescue epinephrine	Favourable
Steill et al [14]	2001	200	IHCA	No difference in 1 hour survival, hospital discharge, neurological deficits	Neutral
Wenzel et al [15]	2004	1219	OOHCA	Higher hospital admission and discharge in vasopressin group with asystole but not in VF or PEA. Rescue therapy with epinephrine resulted in increased survival in vasopressin group	Favourable
Grmec et al [16]	2006	109	OOHCA	Improved ROSC and hospital discharge among MI pts but not overall	Favourable
Malley et al [17]	2007	598	OOHCA	Higher ROSC and 24 hour survival in vasopressin group. Higher discharge rates in asystole subgroup. Better neurological outcome	Favourable
Mukoyama et al [18]	2009	336	OOHCA	No difference in ROSC, 24 hour survival, hospital discharge.	Neutral

Table 2: Summary of studies demonstrating use of vasopressin-epinephrine combination in adults

	Year	Number of Patients	In or out of Hospital cardiac arrest	Results	Conclusion with respect to Combination
Guyette et al [19]	2004	298	OOHCA	Higher ROSC with combination	Favourable
Callaway et al [20]	2006	325	OOHCA	Similar ROSC in both groups	Neutral
Gueugniaud et al [21]	2008	2956	OOHCA	Similar ROSC, survival to admission and discharge, neurological recovery and 1 year survival	Neutral
Mentzelopoulos et al [22]	2009	100	IHCA	Higher ROSC and discharge rates with the combination therapy along with steroids	Doubtful
Cody et al [23]	2010	191		Similar survival, 24 hour survival and discharge	Neutral

Having reviewed the limited evidence available regarding the use of vasopressin in cardiac arrest, the following recommendations can be made:

1. Vasopressin is especially beneficial in asystole and prolonged cardiac arrest, e.g. out-of-hospital cardiac arrest as these states of profound ischemia are accompanied by epinephrine resistance due to down-regulation of catecholamine receptors.

2. Vasopressin may be considered in lieu of one or two doses of epinephrine or in refractory cardiac arrest after 3 doses of epinephrine have been given.

3. For maximal benefit of vasopressin, the simultaneous presence of epinephrine should be ensured. Thus, simultaneous administration of both drugs may be considered or timing of doses should overlap with the t1/2 of the other drug.

Applying evidence to practice

The child may be given vasopressin (0.8 units/kg) in an attempt to restore spontaneous circulation in this situation of refractory cardiac arrest. Effect will be more advantageous if it is given within the t1/2 of the last dose of epinephrine.

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