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Abstract

Background: Vasopressin (VP) shows promise as a pressor agent in animals and adult human cardiac arrest and resuscitation, but has not been studied for pressor effect in critically ill or arrested children. VP infusion is routine treatment for diabetes insipidus during brain death evaluation and organ recovery. We hypothesized that low dose VP infusion during organ recovery in critically ill children exerts a pressor effect, without major organ toxicity. *Methods:* 34 VP-treated and 29 age-matched critically ill controls (C) ≤ 18 years were retrospectively reviewed during brain death evaluation and organ recovery. VP infusion protocol titrated VP dose clinically to urine output, with high variability. Pressor and inotrope management was titrated clinically to BP, cerebral perfusion and central venous pressures (when available) and peripheral perfusion with similar protocol targets for pre-load in VP and C groups. Outcome measures include dose, type and number of pressors and inotropes. Organ function was assessed at recovery and 48 h post-transplant by independent surgeon and transplant program organ function criteria. Analysis by Odds Ratio (OR), and chi-square. *Results:* VP dose averaged 0.041 ± 0.069 U/kg/h. Average baseline mean arterial pressure (MAP) before VP infusion was 79 ± 17 mmHg VP and 76 ± 14 mmHg C ($P = 0.6$). Subsequent average MAP were: 82 ± 21 mmHgVP after VP infusion versus 71 ± 16 mmHg C ($P = 0.01$) and 80 ± 14 mmHg VP versus 68 ± 22 mmHg C ($P = 0.01$). Ability to wean/stop pressors and inotropes was: dopamine (14/23) 42% VP versus (10/26) 38% C ($P = 0.75$), dobutamine (4/7) 57% VP versus (0/6) 0% C ($P = 0.026$), epinephrine (4/5) 80% VP versus (0/6) 0% C ($P = 0.006$), norepinephrine/phenylephrine (4/4) 100% VP versus (2/5) 40% C ($P = 0.057$). Alpha agonist pressor dependence was successfully weaned from 7/9 (78%) VP versus 0/9 (0%) C: odds ratio = 7.3, ($P < 0.01$). There was no VP induced dysrhythmia, hypertension, anuria or toxicity reported. Good organ recovery function was not significantly different at recovery or 48 h post-transplant for kidney (79% VP versus 69% C, $P = 0.068$), liver (87% VP versus 95% C, $P = 0.533$), or heart (90% VP versus 71% C, $P = 0.11$). *Conclusions:* Low dose vasopressin infusion exerts a pressor effect in critically ill children treated for diabetes insipidus during brain death and organ recovery. VP treated patients were 7.3 times more likely to wean from alpha agonists than comparably managed age matched controls, without adverse affect on transplant organ function. We speculate that further prospective assessment of VP safety and efficacy as a pressor adjunct for resuscitation of critically ill children is warranted.

Keywords: Vasopressin; Vasopressor therapy; Pediatric resuscitation; Cardiopulmonary resuscitation (CPR); Brain death; Inotropes

1. Introduction

Survival outcome following cardiac arrest remains dismal despite implementation of advanced cardiac life support interventions. The utility of epinephrine, considered the 'gold standard' drug

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for cardiac resuscitation, has recently been questioned and may be no more effective than placebo in some circumstances [1]. Consequently, alternative therapies have been explored, including the hormone vasopressin (pitressin, antidiuretic hormone, or ADH). Endogenous levels of arginine vasopressin are elevated in patients suffering cardiac arrest, and return of spontaneous circulation is associated with elevated vasopressin levels [2]. In ventricular fibrillation animal models, vasopressin administration results in a very powerful vasoconstrictive effect, increasing coronary perfusion pressure and mean arterial pressure more than epinephrine, while preserving myocardial and cerebral blood flow [3]. Vasopressin enhances myocardial oxygen delivery and increased cardiac contractility without increasing myocardial oxygen demand. The mechanism of vasopressin's action may be related to V1 receptor stimulation and augmentation of endogenous catecholamines [3]. Recently, adult trials of VP treatment of refractory ventricular fibrillation showed promise in terms of increased 24-hour survival compared with those who received epinephrine [2,4]. Vasopressin is reported to significantly increase coronary perfusion pressure in prolonged human pulseless electrical activity (PEA) and asystole during CPR [5]. Additionally, vasopressin administration in porcine PEA models resulted in a significant increase in left ventricular myocardial and cerebral blood flow during CPR and a higher rate of return of spontaneous circulation (ROSC) compared with animals receiving high-dose epinephrine [6]. Endobronchial administration of vasopressin in porcine cardiac arrest models has demonstrated improved resuscitation outcome and survival [7]. Vasopressin has also been investigated as an alternative pressor in adults with septic shock and vasodilatory shock after cardiac surgery, and reduced the need for other catecholamine pressors [8,9].

The use of vasopressin as either a pressor or resuscitation drug in the pediatric population, however, has not been examined. Vasopressin has been used safely and effectively for management of diabetes insipidus, nocturnal enuresis, and gastrointestinal hemorrhage in children [10,11]. The pressor effectiveness has not been independently evaluated previously, and it has not been studied in cardiac arrest or brain death. The Gift of Life Donor Program adopted a protocol titrating vasopressin infusion to treat diabetes insipidus in children meeting clinical brain-death criteria during the organ-recovery period. This population, although not in cardiopulmonary arrest, is often critically-ill and pressor-dependent. The recent reports of vasopressin use in adult resuscitation stimulated a retrospective review of the effect of vasopressin infusion on pressor-dependent children. The purpose of this study was to determine whether low dose vasopressin infusions exerted pressor effects, maintained a stable hemodynamic profile, allowed weaning of other alpha agonists, and preserved organ quality at organ recovery in these patients. This data may encourage appropriate evaluation of vasopressin as an adjunct or alternative pressor medication for use in pediatric cardiopulmonary arrest, resuscitation, and support of critically ill children.

2. Methods

A retrospective case-control study of pediatric organ-recovery patients after brain-death was performed to evaluate the vasopressor effects of low-dose vasopressin infusion treatment of diabetes insipidus. Patient charts reviewed were among those organ-donors 18 years old or younger who met clinical brain-death criteria during the period 1996-1998 in the Gift of Life Donor Program. Families of all patients gave written informed consent for organ recovery and data collection. Thirty-four patients received vasopressin infusions during this time period. Twenty-nine age-matched patients who did not receive vasopressin were identified from the remaining organ donor patients during the same time period and served as controls. Data was obtained from the standard data collection tool routinely employed by the transplant program. Patient confidentiality was maintained throughout the entire review process.

Vasopressin was administered as an infusion via a standardized Gift of Life Donor Program protocol for those patients who met clinical and laboratory criteria for diabetes insipidus. In the absence of alternative etiologies, a clinical definition of diabetes insipidus (inappropriately low urine osmolarity and urine sodium concentration in the presence of elevated serum sodium >155 mmol/l and osmolarity >300 mOsm/l) was used. Fifty units of vasopressin were mixed in 100 ml of normal saline (0.5 U/ml). Vasopressin was infused

at a rate of one to eight units per hour and titrated to maintain a clinically desired urine output. Target urine output was determined and monitored clinically without a universal prospective target flow rate. Vasopressin was not administered or titrated for the primary purpose of hemodynamic support.

The outcome variables compared between the two groups included: differences in MAP, total number of pressors and inotropes (norepinephrine, epinephrine, phenlyephrine, dobutamine and dopamine) at time of recovery, ability to reduce or discontinue pressor and inotrope infusion dose and organ outcome at time of recovery. Organ quality at time of recovery was defined by the Gift of Life Donor Program transplant surgeon report at time of organ recovery. Organ function 48 h after transplant was defined as good, fair or poor by transplant program criteria. Kidney quality was characterized by the evaluation for acute tubular necrosis and post-transplant dialysis requirement. Heart quality characterized by transplant surgeon report and need for post-transplant inotropic support. Liver quality was characterized by serum and plasma liver function tests in the 48-hour post-transplant period. Only those recovered organs where actual transplant was attempted were included in the 48-hour post-transplant data analysis. Statistical analysis was performed using odds ratio and chi-square tests.

3. Results

Thirty-four vasopressin patients and 29 age-matched controls were evaluated. Characteristics of the vasopressin and control groups are shown in Fig. 1. In no instance was the low dose vasopressin infusion discontinued for dysrhythmia, hypertension or other hemodynamically significant adverse effect. The dosages of vasopressin used ranged from 0.0002 U/kg/h to 0.15 U/kg/h, with an average dose of 0.041 U/kg/h (SD 0.069 U/kg/h). No specific cut-off for minimal effective dose within this dose range could be identified. Analysis of the average MAP of the two groups (Fig. 1) revealed a comparable baseline value (79 ± 17 mmHg VP versus 76 ± 14 mmHg C, $P = 0.6$). However, additional values obtained after the start of vasopressin infusion showed a statistically significant difference between the vasopressin and control patients: 82 ± 21 mmHg versus 71 ± 16

	VASOPRESSIN	CONTROL	
Number Patients (n)	34	29	
Thyroxine Protocol	9	3	
Age (avg., yrs)	8.2 +/-6.5	8.9 +/-6.2	
Male	14	15	
Female	20	14	
Weight (avg., kg)	31.4 +/-22.0	36.2 +/-25.6	
MAP (avg., mmHg) **Baseline**	79 +/-17	76 +/- 14	
Pre Organ Recovery	82 +/-21*	71 +/-16	**P<0.01**
At Organ Recovery	80 +/-14*	68 +/-22	**P<0.01**
Dopamine **Wean or off/Total on**	14/33 (42%)	10/26 (38%)	
Norepinephrine (NEPI) or Phenylephrine (PE) **Wean or off/Total on**	4/4 (100%)*	2/5 (40%)	**P<0.05 for PE or NEPI**
Epinephrine **Wean or off/Total on**	4/5 (80%)*	0/6 (0%)	**P<0.01**
Dobutamine **Wean or off/Total on**	4/7 (57%)*	0/6 (0%)	**P<0.05**
Kidney Function **Good/Fair/Poor**	46/2/10	33/8/7	
Heart Function **Good/Fair/Poor**	19/1/1	10/4/0	
Liver Function **Good/Fair/Poor**	27/1/3	21/0/1	

Fig. 1. Table comparing characteristics and critical outcome variables of vasopressin vs. age-matched control patients: inclusive of thyroxine protocol patients.

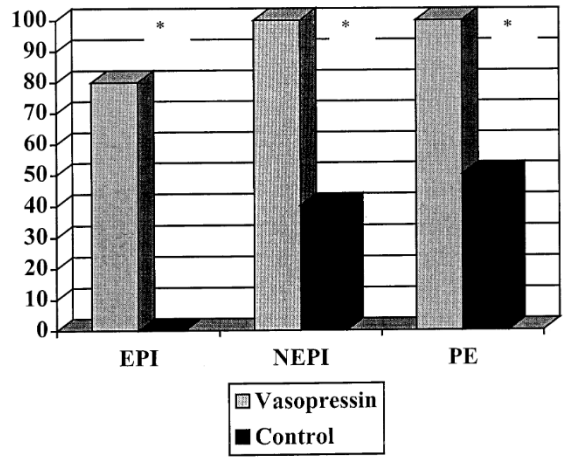

Fig. 2. Percent of vasopressin vs. age-matched control patients able to wean or stop pressors (norepinephrine (NEPI), epinephrine (EPI), phenylephrine (PE)) at time of organ recovery.

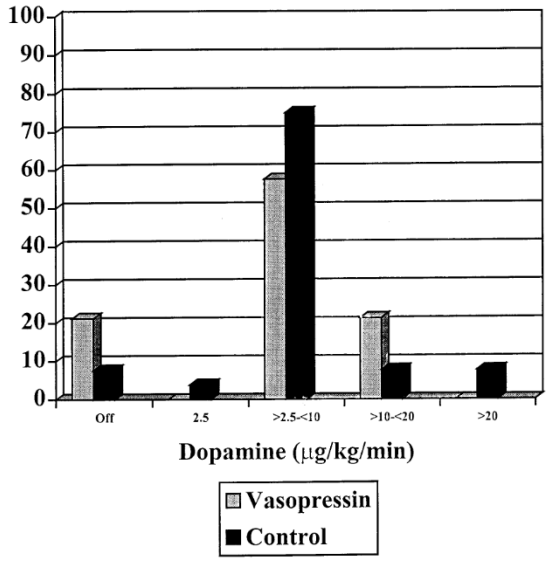

Fig. 3. Percent of vasopressin vs. age-matched control patients on various dopamine dosages at organ recovery (μg/kg/min).

mmHg ($P = 0.01$) and 80 ± 14 mmHg versus 68 ± 22 mmHg ($P = 0.01$). Baseline average urine output was 13.0 ± 14.1 ml/kg/h for the vasopressin group and 6.8 ± 9.0 ml/kg/h for the controls ($P = 0.038$). Subsequent measurements revealed a urine output of 13.37 ± 17.4 ml/kg/h (post-vasopressin infusion) for the vasopressin group and 7.91 ± 9.2 ml/kg/h for the controls ($P = 0.11$).

The number of patients requiring the pressors norepinephrine, epinephrine or phenylephrine for additional blood pressure control at organ recovery was analyzed (Fig. 2). Of the nine vasopressin and nine control patients on these drugs initially, 7/9 (78%) VP and 0/9 (0%) controls were able to wean or stop alpha agonists by the time of organ recovery (OR = 7.3, $P = < 0.01$).

The total number of pressors and inotropes (norepinephrine, epinephrine, phenylephrine, dopamine, dobutamine) required to maintain hemodynamic support at the time of organ recovery was compared for the vasopressin versus control groups. Of the 34 VP patients seven needed no pressors/inotropes (20.5%), 23 required one pressor/inotrope (67.6%), four used two pressor/inotropes (11.7%); no patients in the vasopressin group were maintained on more than two pressor/inotropes. Of the 29 controls four needed no pressor/inotrope (13.7%), 13 needed one pressor/inotrope (44.8%), eight required at least two pressor/inotropes (27.5%) and four were on three pressor/inotropes (13.7%). At the time of organ recovery, significantly more vasopressin patients required $\leq$ one pressor/inotrope ($P = 0.007$) and $\leq$ two pressor/inotropes ($P = 0.025$) than age matched controls.

The next parameter explored involved the ability of the patient, once placed on a pressor/inotrope (norepinephrine, epinephrine, phenylephrine or dobutamine), to either decrease or stop the medication. Four of seven patients (57.1%) in the vasopressin group placed on dobutamine were able to either decrease or stop the drug, compared to none of the six controls (0%, $P = 0.026$). Four of the five vasopressin patients (80%) were able to reduce or discontinue epinephrine; none of the six controls placed on epinephrine were able to wean or stop the drug ($P = 0.006$). Additionally, four of the four patients (100%) placed on either norepinephrine or phenylephrine were able to stop or reduce the medication, whereas only two of the five controls (40%) were able to do so ($P = 0.057$).

The dosages of dopamine (μg/kg/min) used in both the vasopressin and matched controls are reported (Fig. 3). The dosages were divided into: 'off', 2.5 μg/kg/min ('renal'), 2.5–10 μg/kg/min (alpha and beta-agonist), 10–20 μg/kg/min (alpha-agonist), and greater than 20 μg/kg/min ('hemodynamic effects similar to those of norepinephrine') [12]. A total of seven of 33 vasopressin patients (21.2%) and two of the 26 controls (7.6%) were able to stop the dopamine once started ($P = 0.15$). None of the 33 vasopressin children and one of

the 26 controls (3.8%) were on 'renal' dosages of dopamine ($P = 0.325$). Nineteen of 33 vasopressin patients (57.5%) and nineteen of 26 control (75%) patients required dopamine between 2.5 and 10 μg/kg/min of dopamine ($P = 0.568$). Seven of the 33 vasopressin patients (21.2%) and two of the 26 controls (7.6%) were on dopamine doses between 10 and 20 μg/kg/min ($P = 0.10$). None of the 33 vasopressin group and two of the 26 controls (7.6%) were on greater than 20 μg/kg/min of dopamine at the time of organ recovery ($P = 0.105$).

A comparison of organ outcomes between the two groups is presented in Fig. 4. Kidney outcomes reveal that of the 58 kidneys recovered in the vasopressin group, 46 (79.3%) were 'good', two (3.4%) were 'fair' and 10 (17%) were 'poor'. The controls demonstrated that of the 48 organs donated 33 (68.7%) were judged 'good', eight (16.6%) were 'fair' and 7 (14.5%) were 'poor' ($P = 0.068$). Examining results of heart quality demonstrated 19 of the 21 vasopressin children's hearts (90.4%) were 'good' one (4.7%) was 'fair' and one (4.7%) was 'poor'. Ten of the 14 control hearts (71.4%) were 'good', four (28.5%) were 'fair' and none was 'poor' ($P = 0.11$). Comparison of liver quality between the two group showed that of the 31 vasopressin livers donated 27 (87%) were 'good', one (3.2%) was 'fair' and three (9.6%) were 'poor'. Twenty-one of the 22 control livers (95%) were 'good', none were 'fair' and one (4.5%) was of 'poor' quality ($P = 0.533$).

Additionally, nine of the 34-vasopressin patients and three of the 29 controls received a combination of intravenous dextrose, methylprednisolone, insulin and thyroxine as part of the Gift of Life Donor Program pediatric organ donor thyroxine protocol. An infusion of 50 ml of 50% dextrose, two grams of methylprednisolone and 20 units of regular insulin were administered, and an infusion consisting of thyroxine (200 μg in 500ml NSS) was delivered at 25ml (10 μg) per hour. Thyroxine infusions were also titrated to maintain target blood pressure, and levels of other pressors were reduced as much as possible. The protocol was implemented at the 'discretion' of the transplant coordinator for patients requiring multiple pressors and hemodynamic instability. The average MAP in those receiving thyroxine was 80 ± 18 mmHg, and the average MAP of those not included in the thyroxine protocol was 75 ± 21 mmHg ($P = 0.49$). Five of the twelve (41.6%) who received the thyroxine protocol were able to wean or discontinue pressor agents, and nineteen of thirty-four (55.8%) not on the protocol were able to do so ($P = 0.39$). Repeat analysis excluding all children receiving thyroxine protocol corroborated the low probability of independent effect, in this small case series, on pressor and inotrope dependence and organ outcome (see Fig. 5).

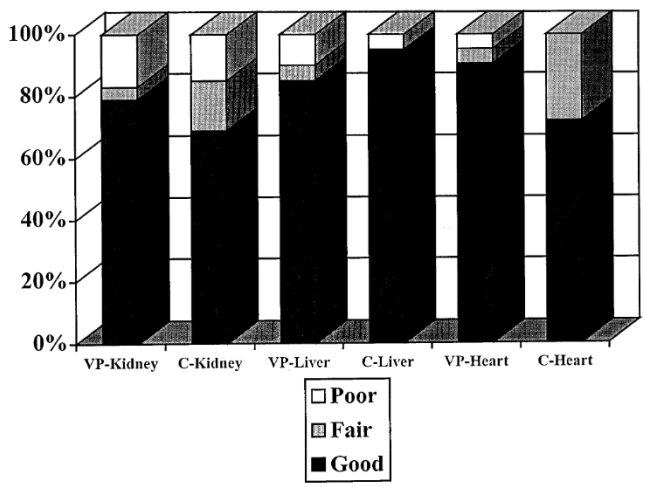

Fig. 4. Comparison of good, fair and poor recovered organ outcome at 48 h after transplantation.

4. Discussion

Vasopressin is a promising vasopressor in adult cardiopulmonary arrest and shock, but no studies to date have explored its use as a vasopressor for resuscitation of children. The specific aim of this retrospective study was to demonstrate low dose vasopressin infusion pressor effects in a critically ill pediatric population who were given the drug as therapy for diabetes insipidus. Arginine vasopressin (VP) is an endogenous neural peptide hormone synthesized and secreted by the posterior pituitary. Vasopressin works via three different receptors: V1a, V1b and V2. The V1a and V1b receptors are both serpentine vascular receptors while the V2 receptors function by increasing cGMP levels. The V1a receptors are found in blood vessels and control the vasoconstrictive effects of vasopressin. The V1b receptors are located in the anterior pituitary and mediate vasopressin-induced increases in ACTH secretion. The V2 receptors are found in the nephron and control the antidiuretic effect of vasopressin. Vasopressin is quickly inactivated by the liver and kidney and

	VASOPRESSIN	CONTROL	
Number Patients (n)	25	26	
Thyroxine Protocol	0	0	
MAP (avg., mmHg)			
Baseline	79±16	77±15	
Pre Organ Recovery	84±20	70±17	**P<0.01**
At Organ Recovery	81±15	66±22	**P<0.01**
Norepinephrine (NEPI) or Phenylephrine (PE) Wean or off/Total on	4/4 (100%)*	1/3 (33%)	**P=0.05 for PE or NEPI**
Epinephrine Wean or off/Total on	2/3 (67%)*	0/5 (0%)	**P<0.03**
Dobutamine Wean or off/Total on	3/5 (60%)*	0/6 (0%)	**P<0.05**
Kidney Function Good/Fair/Poor	36*/0/6	29/8/7	**P< .05 for good function**
Heart Function Good/Fair/Poor	13/1/0	9/4/0	
Liver Function Good/Fair/Poor	19/1/3	19/0/0	

Fig. 5. Table comparing characteristics and critical outcome variables of vasopressin vs. age-matched control patients: exclusive of thyroxine protocol patients.

has a biologic half-life of approximately 18 minutes in humans. Stimulants for vasopressin release include increased plasma osmotic pressure, decreased extracellular volume, pain, stress, drugs (morphine, nicotine, barbiturates, beta-agonists), angiotensin II, hypoxia and hypercapnia. Agents which decrease vasopressin release include decreased plasma osmotic pressure, increased extracellular volume, alpha-agonists, atrial natriuretic peptide and ethanol [13,14].

In this retrospective case series, patients who received low dose vasopressin infusion for diabetes insipidus maintained a statistically significant higher MAP than matched controls. The effect of vasopressin on blood pressure and other hemodynamic variables has been well documented in both animal and adult human CPR studies and may be more potent and longer-lasting than that of epinephrine [15,16]. Vasopressor effects reported in animals and adult humans supports further evaluation of vasopressin use for treatment of hypotension and cardiovascular collapse in children.

The vasopressor effect of even low-dose vasopressin infusion for diabetes insipidus in this case series is demonstrated by the number of pressors required for hemodynamic stability and ability to wean from pressors. Vasopressin may reduce or even obviate the need for other vasoactive medications. Almost 90% of the children who received vasopressin required one pressor or less compared with only 58% of the controls ($P = 0.007$). All of the vasopressin group were maintained on two pressors or less at the time of organ-recovery compared with only 86% of those not treated with vasopressin ($P = 0.025$). In addition the children treated with vasopressin were seven times more likely to wean or discontinue alpha-agonist medications than those in the control group. In patients managed with other supportive medications (norepinephrine, dobutamine, epinephrine or phenylephrine) the vasopressin-treated children were able to reduce or stop these drugs prior to organ recovery significantly more often than those children who did not receive vasopressin. Vasopressin augments cardiac contractility, and this property may explain the fact that both dobutamine and epinephrine could be weaned in $>$ 80% or discontinued in $>$ 50% of those patients treated with vasopressin compared to none of the controls ($P = 0.026$ and 0.006, respectively).

Analysis of dopamine dosage requirement is complex. Dopamine dosage may be difficult to interpret because the dose-response effects of dopamine are variable in children. Experience indicates that what may represent 'renal' doses of dopamine in one patient may behave as a strong pressor in another [17]. Attempted quantitative analysis did not reveal significant differences between VP and control for these dosage ranges, but may have limited capability to detect differences in the context of wide dosage variability.

Organ outcome was the final variable examined in the study. The differences in outcome between the two groups for the kidney, liver and heart were not statistically significant ($P = 0.068$, 0.11 and 0.533, respectively). These results demonstrate, however, that vital organ flow was preserved at least as well while on the vasopressin infusion compared to standard pressor therapy. This notion is supported in animal CPR models in which blood is preferentially shunted away from nonvital organs (skeletal muscle, small intestine) to favor major organs such as the liver, kidney, heart and brain. This effect mediated by vasopressin may be more pronounced than that of epinephrine [3]. The use of vasopressin to support vital organ function may, at the very minimum, parallel the effects of standard pressor therapy.

Potential confounding factors of urine output, intravascular volume, etiology of brain death, and concurrent use of thyroxine, insulin and steroids were difficult to evaluate retrospectively. In this very limited study population the administration of thyroxine, steroid and insulin showed little impact on the ability of either population to reduce or stop vasoactive medications. Analysis excluding all children receiving thyroxine protocol corroborated the low probability of independent effect, in this small case series, on pressor and inotrope dependence and organ outcome. Volume status and urine output were not prospectively titrated to very specific targets, but were managed clinically and accounted for.

In summary, critically ill children meeting criteria for brain death receiving low dose vasopressin infusion maintained a higher average MAP and were able to reduce or discontinue other pressors more often than the controls. Vasopressin also safely preserved critical organ perfusion and function following transplant, when compared to comparable patients receiving conventional catecholamine pressors. These results mirror those found in adult studies of vasopressin being implemented as a pressor in sepsis and vasodilatory shock following cardiac surgery [8,9].

5. Study limitations

There were several study limitations. This was a retrospective study with a limited patient population and only 29 age-matched controls. The population of critically ill children is relatively small compared to adults, which limits the power of the observations. The dose of vasopressin used to control diabetes insipidus in the pediatric population is relatively low and very variable compared to that used for acute cardiac resuscitation or treatment of gastrointestinal hemorrhage in adults (0.4–0.8 units/kg). In addition a pressor dose of vasopressin has not been clearly identified in the pediatric population. However, we speculate that higher doses would be expected to exert an even greater pressor effect than the low dose vasopressin dosing reported in this study. Another limitation is that more invasive and comprehensive hourly data on fluid balance and intravascular volume were not consistently collected in a prospective manner, making more in-depth comparison of pre-load impractical. A consistent methodology for estimate of effective circulating volume in both groups of patients with complex fluid balance issues (e.g. diabetes insipidus, shock, traumatic brain injury, and hypovolemia) was not enforced prospectively. The volume status of both the vasopressin and control patients may impact the ability to wean or discontinue pressor agents. Invasive hemodynamic monitoring was not frequently performed because of the relative difficulty and impracticality of invasive monitoring in children. However, transplant coordinators have similar clinical goals and targets for management of brain dead children during organ recovery.

Another limitation of the study is that data concerning organ outcome may be subjective and difficult to interpret, since many of the adverse outcomes may have resulted from recipient problems and not the donor. Nevertheless, there was not a demonstrable difference in subjective organ outcomes between the vasopressin and control groups. Description of the recipient's medical condition at the time of transplant, as well as long-term organ-outcome data, may be helpful to obtain in future studies. Also, though all of the patients included met clinical brain-death criteria, the etiology of the brain-death was not uniform, which may further influence pressor utilization and outcomes. Furthermore, those children with diabetes insipidus or requiring thyroxine, insulin and glucose therapy may represent a potentially different or sicker patient subset than other critically ill children. Despite these caveats, it appears that vasopressin exerted a powerful pressor effect.

6. Conclusions

This retrospective, case-control series suggests that low dose vasopressin infusion exerts significant vasopressor effects without significant toxicity in critically ill children during evaluation for brain death and organ recovery. Further prospective studies are justified to further define vasopressin's role as a pressor and resuscitation drug in the critically ill pediatric population.

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