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Nameet Jerath
Helena Frndova
Brian W. McCrindle
Rebecca Gurofsky
Tilman Humpl

Clinical impact of vasopressin infusion on hemodynamics, liver and renal function in pediatric patients

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N. Jerath · H. Frndova
University of Toronto, Department of Critical Care Medicine,
555 University Avenue, M5G1X8 Toronto ON, Canada

B. W. McCrindle · R. Gurofsky · T. Humpl (✉)
University of Toronto, Hospital for Sick Children, Department of Pediatrics, Division of Cardiology,
555 University Avenue, M5G1X8 Toronto ON, Canada
e-mail: tilman.humpl@sickkids.ca
Tel.: +1-416-8136477
Fax: +1-416-8137299

T. Humpl
University of Toronto, Hospital for Sick Children, Department of Critical Care Medicine,
555 University Avenue, M5G1X8 Toronto ON, Canada

Abstract *Objective:* To study effects of vasopressin on hemodynamic, clinical, and laboratory variables in children with advanced vasodilatory shock. *Design and setting:* Retrospective study in a multidisciplinary tertiary pediatric critical care unit. *Patients and participants:* Patients ($n = 117$; 32 noncardiac, 85 postcardiac surgery) requiring intravenous vasopressin infusion longer than 60 min for advanced shock (January 2004 to December 2005). *Interventions:* Vasopressin infusion ($n = 157$). *Measurements and results:* Both cardiac and noncardiac patients showed a significant decrease in inotrope requirement without change in central venous saturation or lactate during infusion. Both groups had increased urea and creatinine and decreased urine output with longer duration/higher cumulative dose of vasopressin. There was a significant increase in conjugated bilirubin level in the noncardiac group during vasopressin infusion; noncardiac patients showed higher AST levels with higher cumulative dose or longer duration of infusion. Postcardiac surgical patients showed a trend towards normal INR values which persisted after vasopressin infusion. Platelet counts were significantly lower during infusion in both groups. *Conclusions:* Vasopressin infusion improved the hemodynamic state in advanced shock without compromising cardiac function. Urine output and creatinine levels were adversely affected but were reversible. This effect was more pronounced with higher dose or duration of infusion. There was no major effect on liver function but a significant reduction in platelet counts. These data suggest that vasopressin is useful in states of vasodilatory shock with limitations regarding to its adverse renal effects and on platelet counts.

Keywords Vasopressin · Vasodilatory shock · Inotrope score · Children · Renal function

Introduction

Vasodilatory shock is a state of pathological vasodilatation, relative or absolute hypovolemia, myocardial depression, and altered blood flow distribution due either to an infection or to the inflammatory responses of the body [1]. Current management principles of vasodilatory shock focus on specific treatment of underlying disease together with volume resuscitation and the use of vasopressors to restore arterial blood pressure [2]. Catecholamines continue to be the first line of vasopressors to be used in such a condition. Unfortunately, it is common to find decreased responsiveness to increasing doses of catecholamines and subsequent side effects.

Ever since Landry et al. [3] reported a state of relative vasopressin deficiency in vasodilatory shock, there has been increased interest in its use as a pressor in states of advanced vasodilatory shock. Various reports also describe a state of relative vasopressin deficiency in advanced septic shock [4, 5]. Vasopressin has a dose-dependent effect

on the arterial system and is a potent vasopressor which is more potent than norepinephrine on a molar basis [6]. Directly it acts on the V1 receptors and phospholipase C mediated vasoconstriction of the smooth muscle in a dose-dependent fashion [7]. Indirectly it enhances the sensitivity of the vasculature to the effects of catecholamines potentiating the contractile effects of catecholamines and its vasoconstrictor effects seem to be preserved during hypoxia and acidosis [2, 8]. These characteristics make vasopressin a good choice in advanced vasodilatory states of shock.

Although there is enthusiasm about its beneficial effects in catecholamine-resistant shock states, concerns have been raised about its potential adverse effects. Vasopressin use has been associated with a significant increase in liver function tests and lactate and decreased cardiac index in adults [9, 10]. There have been variable reports on its effect on renal function and urine output [10–12]. Concerns have also been raised about decreased gastrointestinal blood flow and alterations in the coagulation pathway with its use [9]. Recently there have been several reports of vasopressin use in adult vasodilatory shock states, both cardiogenic and noncardiogenic, but there is still paucity of data about its use in the pediatric population. Most of the available pediatric data are from small case series [11–15]. We undertook this retrospective study to characterize the use and assess the clinical impact of intravenous vasopressin in advanced vasodilatory shock states in children.

Materials and methods

We examined the electronic records of all 3,578 patients admitted to our tertiary multidisciplinary pediatric intensive care between January 2004 and December 2005 who received an infusion of vasopressin for at least 60 min for vasodilatory shock states. Patients who received only a bolus dose or received vasopressin for gastrointestinal hemorrhage or had infusions for less than 60 min were excluded from further analysis.

In general, vasopressin use was reserved for patients with vasodilatory and hypotensive states refractory to the usual inotropes and vasopressors such as epinephrine, norepinephrine, and dopamine, but the use of vasopressin as a vasopressor was ultimately at the discretion of the attending physician.

Data extraction

General data such as age, weight, underlying condition, and hospital mortality were noted for all patients. The electronic charts of all patients included in the review were analyzed in detail for various hemodynamic and biochemical parameters. This included heart rate, systolic and diastolic blood pressure, lactate and central venous oxygen saturation, serum urea and creatinine, liver enzymes (aspartate aminotransferase, AST; alanine aminotransferase, ALT), conjugated and unconjugated bilirubin level, platelet count and international normalized ratio (INR). In addition, data on hourly urine output were collected as were those on platelet transfusions. Both hemodynamic and biochemical variables were collected for three time periods: before, during, and after vasopressin infusion. The dose of other inotropic and vasoactive agents were collected from the charts, including dose and duration of vasopressin. Available results of echocardiograms of the included subjects were reviewed. Systolic and diastolic blood pressure values were converted to percentiles for age and height according to formulae published elsewhere [16]. An inotrope score was calculated based on the dose of various inotropes used. (Dopamine and dobutamine: 1 point for each 1 μg/kg per minute; epinephrine, norepinephrine and isoprenaline: 100 points for each 1 μg/kg per minute; milrinone: 15 points for each 1 μg/kg per minute) [17].

Data analysis

Data are presented as frequency, median (range), or mean (standard deviation) as appropriate. To adjust for lack of independence, since some patients had more than one infusion period, linear regression analysis adjusted for repeated measures with a compound symmetry covariance structure was used to compare the values of all measured dependent variables during vasopressin administration to time points both before and after administration. Analysis was stratified by cardiac vs. noncardiac patients. Linear regression analysis adjusted for repeated measures, also by compound symmetry covariance structure, was used to determine the relationship between dependent variables over time and properties of vasopressin administration. These models were all adjusted for patient type (cardiac vs. noncardiac). For all variables with skewed distribution appropriate mathematical transformations were applied. All analyses were performed using SAS statistical software version 9.1 (SAS Institute, Cary, N.C., USA).

Results

We identified 117 patients receiving 157 vasopressin infusions: 85 postcardiac surgery patients (group A) receiving 125 infusions (up to seven per patient) and 32 noncardiac patients (group B) receiving a single infusion each; patient characteristics are presented in Table 1. There were 19 deaths (22%) in group A and 13 in group B (41%); 13 of the deaths in group A and all deaths in group B occurred while on vasopressin infusion. The median dose was 1.04×10^{-4} U/kg per minute ($0.48–9.80 \times 10^{-4}$) in group A and 2.48×10^{-4} U/kg

Table 1 Patients characteristics in patients after cardiac surgery (*group A*; $n = 85$) and in noncardiac patients (*group B*; $n = 32$)

	Group A	Group B
Age, mean (range)	12.5 months (1 day–13.5 years)	9 years (1.9 months–17.5 years)
Sex: M/F	51/34	16/16
Weight, mean (range; kg)	6.6 (1.32–58.2)	35.7 (3.5–95)
Surgical procedure/underlying condition		
Arterial switch operation[a]	14	–
Modified Blalock-Taussig shunt	10	–
Teratology of Fallot repair	9	–
Norwood procedure	7	–
Bidirectional cavopulmonary connection	7	–
Atrioventricular septal defect repair[a]	6	–
Cardiac transplantation	6	–
Right ventricle to pulmonary artery conduit[a]	6	–
Valve repair/replacement (aortic, pulmonary)[a]	5	–
Pulmonary artery banding, ductal stent	4	–
Total anomalous pulmonary vein repair	3	–
Interrupted aortic arch repair	2	–
Single ventricle palliation (Sano modification)	2	–
Others	6	–
Septic shock	–	10
Trauma, polytrauma	–	5
Cardiomyopathy	–	4
Hepatic failure	–	2
Brainstem tumor	–	1
Bronchiolitis	–	1
Cystic fibrosis	–	1
Arrhythmia	–	1
Leukemia	–	1
Lung transplant	–	1
Meningitis	–	1
Myocarditis	–	1
Pulmonary hypertension	–	1
Rye syndrome	–	1
Suicide attempt	–	1

[a] Including complex cases

per minute ($0.95–9.00 \times 10^{-4}$) in group B. The median infusion time was 24 h (1–416) in group A and 18 h (1–274) in group B. The mean duration of prevasopressin infusion was 12 days (0–96) in group A and 7 days (0–99) in group B. The mean duration of postvasopressin infusion analysis was 22 days (0–140) in group A and 4 days (0–21) in group B. A concomitant milrinone infusion was administered in the following cases: (a) before the vasopressin infusion period: group A in 100 cases (80%; mean dose 0.76 $\mu g\,kg^{-1}\,min^{-1}$, range 0.27–1.1) and group B in 11 cases (34%; mean 0.53, range 0.25–1.0); (b) during the vasopressin infusion period: group A in 87 cases (70%; mean 0.73, range 0.3–1.1) and group B in 6 cases (19%; mean 0.45, range 0.33–0.68); (c) after the vasopressin infusion period: group A in 83 cases (78%; mean 0.67, range 0.32–1.10.73) and group B in 6 cases (32%; mean 0.45, range 0.33–1.0).

Comparison of time periods

Compared to the values before the infusion, there was a significant increase in urea and creatinine and a significant decease in inotrope score, platelets, and unconjugated bilirubin during the infusion in both groups. There was a significant increase in systolic blood pressure a significant decrease in urine output and INR only in group A and a significant increase in conjugated bilirubin only in group B. Neither patient population experienced changes in heart rate, diastolic blood pressure, central venous oxygen saturation (CVO_2), lactate, ALT, AST, hemoglobin, or white cell count between the times before and during the infusion (Tables 2, 3).

Comparing values during the infusion to those after, there was a significant increase in diastolic blood pressure and a significant decrease in heart rate in both groups. Patients in group A experienced a significant decrease in lactate, creatinine, AST, and INR and a significant increase in urine output and CVO_2 which were not seen in group B. A significant decrease in inotropic score and an increase in systolic blood pressure were seen in group B but not in group A. Neither group experienced changes in urea, ALT, conjugated or unconjugated bilirubin, hemoglobin, white cell count, or platelets between the times during and after the infusion.

Table 2 Vasopressin infusion in postcardiac surgery patients ($n = 125$) (*BP*, blood pressure; *BUN*, blood urea nitrogen; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *INR*, international normalized ratio)

	Before infusion		During infusion		After infusion		*p*	
	n	Value	*n*	Value	*n*	Value	Before vs. during	During vs. after
Inotropic score[a]	125	15 (0–221)	122	11 (0–9)	110	10 (0–42)	0.0003	0.43
Heart rate (beats/min)[b]	125	148 ± 18	125	148 ± 9	125	142 ± 20	0.93	0.0002
Systolic BP, percentile[a]	125	10 (< 1–100)	118	14 (< 1–100)	109	16 (< 1–100)	0.06	0.10
Diastolic BP, percentile[a]	122	61 (< 1–100)	104	55 (1–100)	110	65 (1–100)	0.65	0.01
CVO_2 (%)[b]	110	54 ± 13	118	57 ± 14	107	59 ± 11	0.08	0.04
Lactate (mmol/l)[a]	119	2.1 (0.9–16)	124	2.1 (0.9–20)	115	1.5 (0.7–9.7)	0.92	< 0.0001
Urine output (ml kg^{-1} h^{-1})[a]	121	3.4 (0.1–17.2)	120	1.8 (0.2–19)	113	5.4 (0.1–27)	0.0003	< 0.0001
BUN (mmol/l)[a]	107	5.9 (0.8–2)	100	8.4 (0.9–48.7)	114	7.8 (1–60.4)	< 0.0001	0.36
Creatinine (μmol/l)[a,c]	116	52 (21–171)	104	61 (18–224)	114	52 (23–265)	0.0002	0.01
ALT (μ/l)[a,c]	75	26 (5–804)	61	24 (6–763)	88	21 (3–1251)	0.54	0.68
AST (μ/l)[a,c]	81	65 (12–1344)	64	70 (11–1657)	89	43 (12–1062)	0.93	0.05
Conjugated bilirubin (μmol/l)[a,c]	78	1 (0–290)	62	4 (0–176)	78	2 (0–384)	0.28	0.51
Unconjugated bilirubin (μmol/l)[a,c]	71	31 (0–249)	56	17 (0–203)	71	20 (1–225)	0.0006	0.65
Hemoglobin (g/l)[b]	124	128 ± 16	113	128 ± 18	113	130 ± 15	0.68	0.80
INR[b,d]	118	2.0 ± 1.0	90	1.7 ± 0.6	102	1.6 ± 0.7	0.03	0.04
White cell count ($\times 10^9$ g/l)[a,c]	124	10.6 (2.9–67.3)	113	11.9 (2.4–58.2)	113	11.4 (3.1–74.9)	0.21	0.12
Platelets ($\times 10^9$ g/l)[a,c]	123	152 (39–576)	114	140 (18–514)	113	138 (17–431)	< 0.0001	0.33

[a] Median (range)
[b] Mean ± standard deviation
[c] After log-transformation of dependent variable to attain normality
[d] After inverse transformation of dependent variable to attain normality

Table 3 Vasopressin infusion in noncardiac patients ($n = 32$) (*BP*, blood pressure; *BUN*, blood urea nitrogen; *ALT*, alanine transaminase; *AST*, aspartate transaminase; *INR*, international normalized ratio)

	Before infusion		During infusion		After infusion		*p*	
	n	Value	*n*	Value	*n*	Value	Before vs. during	During vs. after
Inotropic score[a,c]	32	19 (0–326)	24	11 (0–122)	16	5 (0–50)	0.03	0.0001
Heart rate (beats/min)[b]	32	133 ± 17	32	130 ± 19	32	118 ± 24	0.42	0.002
Systolic BP, percentile[a]	32	24 (< 1–100)	27	30 (< 1–100)	20	73 (< 1–100)	0.73	0.001
Diastolic BP, percentile[a]	30	13 (< 1–91)	25	14 (< 1–93)	19	32 (< 1–94)	0.41	0.06
CVO_2 (%)[a]	21	67 ± 16	19	70 ± 18	13	73 ± 11	0.97	0.45
Lactate (mmol/l)[a,c]	30	3.2 (1–17.9)	30	3.5 (0.7–24)	20	1.8 (0.8–21)	0.44	0.07
Urine output (ml kg^{-1} h^{-1})[a,c]	29	2.6 (0.2–18.7)	27	1.7 (0.1–11.3)	21	2.1 (0–7.7)	0.12	0.69
BUN (mmol/l)[a,c]	31	8.1 (1.1–44)	22	10 (2.3–27.3)	18	8.3 (1.3–27.6)	0.01	0.86
Creatinine (μmol/l)[a,c]	31	68 (24–681)	22	80 (34–382)	18	58 (28–724)	0.02	0.19
ALT (μ/l)[a,c]	28	70 (16–1411)	16	70 (13–3460)	15	58 (26–2322)	0.12	0.73
AST (μ/l)[a,c]	26	119 (17–3283)	17	130 (16–8475)	17	87 (22–2742)	0.15	0.30
Conjugated bilirubin (μmol/l)[a,c]	27	1 (0–630)	18	16 (0–669)	16	0 (0–134)	0.001	0.43
Unconjugated bilirubin (μmol/l)[a,c]	28	8 (0–296)	19	8 (0–330)	15	7 (1–23)	0.04	0.88
Hemoglobin (g/l)[b]	31	107 ± 20	26	103 ± 18	19	107 ± 19	0.40	0.91
INR[b,d]	30	1.7 ± 0.8	23	1.7 ± 0.7	16	1.5 ± 0.7	0.74	0.33
White cell count ($\times 10^9$ g/l)[a,c]	31	12.5 (0.5–27.1)	26	13.2 (0.6–34.4)	19	11 (0.4–46)	0.92	0.36
Platelets ($\times 10^9$ g/l)[a,c]	31	128 (30–424)	26	109 (31–384)	19	135 (30–333)	0.04	0.57

[a] Median (range)
[b] Mean ± standard deviation
[c] After log-transformation of dependent variable to attain normality
[d] After inverse transformation of dependent variable to attain normality

Relationship to dose characteristics

Controlling for the type of patients (cardiac vs. noncardiac), a higher total vasopressin dose given over the period of the infusion was associated with higher inotropic score ($p = 0.05$), lactate ($p = 0.0007$), AST ($p = 0.05$), and platelets ($p = 0.01$) and with lower CVO_2 ($p = 0.0001$), urine output ($p = 0.002$), and blood urea nitrogen ($p = 0.04$). Postinfusion a longer duration of infusion was associated with higher inotropic score ($p = 0.0005$), lactate

($p = 0.008$), creatinine ($p = 0.004$), AST ($p = 0.006$), and INR ($p = 0.05$) and with lower urine output ($p = 0.05$). Postinfusion a higher maximum rate of infusion was associated with higher inotropic score ($p = 0.0002$), lactate ($p = 0.0008$), INR ($p = 0.03$), and lower CVO_2 ($p = 0.001$) and with urine output ($p < 0.0001$). Hemoglobin and white cell count were not found to be associated with vasopressin dose. Physiological response to vasopressin dose was similar between the two groups, in addition to ALT, AST, and INR which varied in group B but not in group A.

There were 61 events of platelet transfusion among the 125 vasopressin infusions in group A and 11 such events among the 32 infusions in group B. There was no significant relationship between transfusions and vasopressin infusion duration. Renal replacement therapy was needed in 20 of 85 cardiac patients (24%) and in 7 of 32 noncardiac patients (22%) who received vasopressin. Overall 58 received steroids, but with no significant relationship between dose and vasopressin infusion duration. Echocardiography carried out in 186 patients in group A showed qualitatively reduced myocardial function in 25 of 84 (30%) performed before the infusion, 12 of 50 (24%) during the infusion, and 13 of 52 (25%) after the infusion. Echocardiography carried out in 42 patients in group B showed qualitatively reduced myocardial function in 13 of 21 (62%) performed before infusion, 7 of 12 (58%) during the infusion, and 1 of 9 (11%) after the infusion.

Discussion

These data present a retrospective review of vasopressin use in the pediatric critical care population which, to our knowledge, is the largest series published so far. Vasopressin infusion is very effective in improving the hemodynamic status. The requirement of inotropes was significantly reduced during vasopressin infusion in both cardiac and noncardiac groups as reflected by the change in inotrope scores. The inotrope scores continued to show a significant decrease in the noncardiac group, with significant increase in both systolic and diastolic blood pressures even after the stopping of vasopressin infusion. The cardiac group showed a trend towards significant increase in systolic blood pressures during infusion. This reflects the improved hemodynamic state with vasopressin as it allowed weaning from the vasopressors while maintaining the blood pressure.

The improved cardiovascular state with vasopressin infusion and significant reduction in other vasopressor use has been reported earlier [10, 15], as well as an increase in blood pressure with its use [2, 11, 13, 15, 18]. Masutani et al. [13] reported minimal benefits of vasopressin as a vasopressor when used in a small series of very sick children progressing to multiple organ failure. Rodriguez-Nunez et al. [19] have reported similar effects with a vasopressin analogue terlipressin. We demonstrated a trend towards improved systolic blood pressures in postsurgical cardiac patients. The decreased requirements for inotropes were seen in both groups.

Central venous oxygen saturation is a useful estimate of MVO_2 [10, 20–22]; we used CVO_2 as a marker of cardiac index and systemic oxygen supply. No increase in pulmonary vascular resistance has been reported in adult patients on low-dose vasopressin [14]. There have been some concerns of reduced cardiac index in patients receiving vasopressin, prompting investigators to caution its use in cardiogenic shock [10, 15]. However, others have reported no change in cardiac index [9]. We found no significant change in CVO_2 with vasopressin infusion in either the cardiac or noncardiac groups. Lactate levels also changed insignificantly. After the vasopressin infusion period both CVO_2 and lactate levels improved significantly in postcardiac surgery patients, likely reflecting the improved hemodynamic status.

We found a significant decrease in urine output during vasopressin infusion in postcardiac surgery patients which improved significantly after the infusion period. Although there was no such decrease noncardiac patients, we found a significant increase in blood urea and creatinine in both groups. After the infusion period creatinine levels improved significantly in the cardiac group. Vasopressin has so far been shown to have variable effects on the urine output and renal function [10–13, 23, 24]. Vasopressin is thought to improve renal perfusion by its effect on efferent arteriolar vasoconstriction and nitric oxide mediated vasodilatation of the efferent arterioles [25, 26]. However, at higher doses profound vasoconstriction causes decreased renal blood flow [27].

We noted significant observations on further analysis of vasopressin dose and duration. Longer duration of vasopressin infusion, a higher maximum dose of infusion, and a higher cumulative dose of vasopressin were all associated with significantly lower urine output. A longer duration of infusion was associated with a higher creatinine level. These were seen in both cardiac and noncardiac patients. These results show an adverse effect of vasopressin on both urine output and renal functions in the sick pediatric patients.

Vasopressin infusion has been associated with a worsening of liver function tests attributed to vasopressin-mediated reduction in hepatic blood flow or a direct impairment of hepatocellular functions [2]. It is also speculated that more prolonged hypotension before the start of vasopressin may be the cause of pronounced hypoxic hepatitis in some patients [18]. Recently it has been shown that previously adequate fluid resuscitation preserves the splanchnic circulation during vasopressin infusion [2, 28].

There was a significant decrease in unconjugated bilirubin levels in both groups but a significant increase in only the conjugated bilirubin level in the noncardiac group during the vasopressin infusion. There was no significant

change is AST or ALT levels in either group during the infusion. We observed a significant fall in AST levels after the vasopressin infusion in the cardiac group but without any significant change in ALT values. This could reflect an adequately replete intravascular volume of patients as the central venous pressures are continuously monitored and acted upon and hence possibly a maintained splanchnic circulation.

INR values normalized significantly during vasopressin infusion and continued to show a significant improvement after the infusion was discontinued in the postcardiac surgery group, an effect not seen in the noncardiac group. This is in contrast to the earlier reports of no effects on prothrombin time with vasopressin infusion [29]. The opposite effect is observed when the dosage variables are analyzed with longer duration or higher maximum dose, both of which were associated with significantly higher INR values in the noncardiac group. We also found significantly higher AST levels in patients receiving higher cumulative dose or longer duration of infusion. Vasopressin use in higher doses may not be without any hepatic adverse effects. Platelet counts have consistently been found to be lower with vasopressin infusion [9, 18, 29]. This is thought to be effected by V1 receptor stimulation facilitating platelet aggregation and adhesion [30]. We also found a significant reduction in platelet counts during vasopressin infusion in both groups. Milrinone is frequently used because of its positive inotropic and minimal chronotropic properties, and most of the patients in this retrospective study were also on concomitant milrinone infusions. It is also known that milrinone reduces systemic and pulmonary resistance. However, the precise impact of milrinone on vasoplegia is difficult to determine, especially given the extended half-life of the drug.

Comparing potential downsides and benefits of vasopressin to another vasoconstrictor such as norepinephrine on various organ systems shows that high rates of exogenous catecholamines (including norepinephrine) may induce pulmonary edema by increasing filtration and microvascular pressure [31], which is not reported for vasopressin. Possible disadvantages with the use of norepinephrine include the potential for ventricular arrhythmias, especially in patients with left ventricular failure [2, 32, 33]. This could be obviated by using vasopressin, as demonstrated by Lechner et al. [34]. Kidney function is potentially improved by vasopressin as well as by norepinephrine [33], whereas there no human study has clearly demonstrated any advantage or distinct harmful effects of norepinephrine over vasopression on gut perfusion in septic patients. A new scoring system for the use of catecholamines, vasoconstrictors, and phosphodiesterase inhibitors type 3 may provide better insight on properties of vasopressin.

The study has its limitations because of its retrospective nature. We did not measure vasopressin levels, which would have been useful. It is difficult to determine the exact impact of vasopressin on blood flow in various regions of the body, and some measurements may reflect changes at different points in time. A properly designed prospective randomized control trial is needed to provide strong scientifically based evidence for the efficacy of vasopressin in advanced states of vasodilatory shock.

In conclusion, we found vasopressin infusion to be very useful in improving the hemodynamic state in advanced vasodilatory shock with decreased inotrope requirement while maintaining CVO_2. It reduced urine output and worsens plasma creatinine levels, which were both reversed on stopping the infusion. This effect was more pronounced with higher dose or duration of infusion. It had no major effects on liver functions but did cause a significant reduction in platelet counts. These data suggest that vasopressin is useful in states of vasodilatory shock although there are limitations with regards to its adverse renal effects and platelet counts.

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