VASOPRESSIN VERSUS NOREPINEPHRINE IN PATIENTS WITH VASOPLEGIC SHOCK AFTER CARDIAC SURGERY: THE VANCS RANDOMIZED CONTROLLED TRIAL

Ludhmila Abrahão Hajjar et al

Supplement

Surgical and anesthetic procedure

In the operating room, all patients had a central venous catheter and invasive arterial catheter placed. Cardiac output was measured using a minimally invasive monitor based on pulse contour analysis (Vigileo Flo Trac, Edwards Lifescience, Irvine, CA, USA). In patients with an intraaortic balloon pump, cardiac output was measured using a pulmonary artery catheter (Vigilance II, Edwards Lifescience). Anesthesia was administered according to an institutional protocol, and included induction with fentanyl (3-5 μg/kg), midazolam (0.05 mg/kg), etomidate (0.2-0.3 mg/kg), and pancuronium bromide (0.1 mg/kg), and maintenance with isoflurane in oxygen and fentanyl as needed. During CPB, additional doses of midazolam and pancuronium were administered as required. Methylprednisolone (10 mg/Kg) and cefuroxime (750 mg) were administered intravenously at induction of anesthesia.

After tracheal intubation, all patients received invasive mechanical ventilation with intermittent positive pressure with a tidal volume of 6 mL/kg, positive end-expiratory pressure (PEEP) of 5 to 8 cm H_2O, and fraction of inspired oxygen of 0·6 to 1 to keep the arterial oxygen saturation greater than 95%. Nitroglycerin or sodium nitroprusside were administered intravenously as vasodilators and dobutamine as an inotrope. Blood glucose levels were kept less than 160 mg/dL (8·9 mmol/L), using a continuous insulin infusion if needed. All surgical procedures were undertaken through a median sternotomy. All patients received 5 g of ε-aminocaproic acid as antifibrinolytic, at induction of anesthesia and an additional 1 g/h until the end of surgery. Anticoagulation was established with an initial dose of 500 IU/kg of heparin injected into the central venous line before initiation of bypass with a target activated clotting time of 480 seconds. At the end of bypass, heparin was reversed by protamine chloride initially in a 1:1 ratio, with additional doses as required to return the activated clotting time to preoperative values.

The CPB involved a centrifugal pump (Medtronic Biomedicus; Medtronic, Minneapolis, Minnesota) and a microporous polypropylene membrane oxygenator (Braile; São José do Rio Preto, São Paulo, Brazil) with an integrated venous cardiotomy reservoir. The oxygenator was primed with 1500 mL of lactated Ringer solution, 20% (1 g/kg) mannitol, and 2500 units of unfractionated heparin. During CPB, a mild hypothermic temperature management strategy (32°C to 34°C) with α-stat blood gas management was used in all

patients. Nonpulsatile flow was maintained at 2·0 to 2·4 L/min/m^2 and MAP varied from 60 to 90 mmHg. Myocardial preservation was achieved by intermittent antegrade cold crystalloid cardioplegia. Cardioplegia was repeated every 30 minutes during the cross-clamping period. Lactated´s Ringer solution was infused according to filling pressures, diuresis, and cardiac output. Colloids were not used during the study period.

Data collection and definitions

We recorded the following preoperative laboratory values, collected within 48 hours prior to surgery: haemoglobin, hematocrit, prothrombin time, activated partial thromboplastin time, creatinine level, bilirubin level, and platelet count. We also collected data related to characteristics of the surgical procedure including type of surgery, number and type of grafts used, duration of CPB and aortic cross-clamping, type and amount of fluid (including blood transfusions), and laboratory data during the intraoperative period, such as hemoglobin levels and haematocrit at baseline (just after induction of anesthesia), during CPB, and at the end of the procedure, central venous oxygen saturation ($ScvO_2$) and lactate concentration at the beginning and at the end of the procedure.

In the first 89 patients, we measured serum vasopressin levels immediately and 6, 12 and 24 hours after drug infusion. Blood samples were collected and stored in refrigerated tubes containing ethylenediaminetetraacetic acid (EDTA) and the plasma was stored at -70o C until analysis. Aprotinin (Trasylol®, Bayer, Germany) at 500 KUI was added per mL. Vasopressin was analyzed after extraction on reversed phase column by double antibody immunoassay (Buhlman Laboratories, Basel, Switzerland) at InCor Laboratory, Faculty of Medicine – University of São Paulo. The sensitivity limit of this assay is 0.39 pmol/L.

During the ICU stay, all patients were assessed daily by investigators and clinical and laboratory data were recorded. Organ failure was assessed using the Sequential Organ Failure Assessment (SOFA) score,[1] calculated using the worst values within the first 24 hours after ICU admission. Haematocrit, C-reactive protein (CRP), platelet count, serum creatinine, troponin, creatine kinase-MB, bilirubin, arterial lactate, and $ScvO_2$ were collected at least daily. An electrocardiogram was performed daily.

During 30 days, we evaluated the incidence of mortality or severe complications including stroke, requirement of mechanical ventilation for longer than 48 h, deep sternal wound infection, reoperation or acute renal failure. We also evaluated the 30-day incidence of infection, septic shock, arrhythmias (atrial fibrillation and ventricular arrhythmia), duration of mechanical ventilation, hemodynamic effects (the time to attainment of hemodynamic stability, the changes in hemodynamic variables, and the use of dobutamine or other vasoactive agents), incidence of adverse events (hyponatremia, acute myocardial infarction, digital ischemia and acute mesenteric ischemia) and ICU and hospital lengths of stay. We

also evaluated 30-day incidence of pulmonary embolism, low cardiac output syndrome, acute respiratory distress syndrome (ARDS), delirium, stages of acute kidney injury (AKI) according to AKIN criteria. About the AKI definition, in our study, we used SCr only and not urine output because in cardiac surgery, we use mannitol to wean off cardiopulmonary bypass and furosemide quite regularly during the ICU stay, so that we are concerned about a possible impact of these interventions on urine output.

Acute myocardial infarction was defined as at least one of the following findings associated with clinical symptoms suggestive of myocardial ischemia: an increase or decrease in cardiac troponin I, with at least one value above the 99th percentile of the upper reference limit; electrocardiographic changes, such as new Q waves, ST-elevation, or a new left branch block; or image-based evidence of new loss of viable myocardium.[3]

Low cardiac output syndrome was defined as a cardiac index less than 2.2 L/min/m^2 associated with impaired end-organ perfusion, as reflected by at least one of the following: altered mental status, cold extremities, oliguria or metabolic acidosis or $SvcO_2$ < 65%.[4]

Delirium[5] was diagnosed if the Confusion Assessment Method for the ICU (CAM-ICU) was positive during the ICU stay.

Renal function was evaluated daily (eTable 5 and eTable 6).[8,9] Mesenteric ischemia was defined as an occlusive or non-occlusive impairment of intestinal blood flow diagnosed by arteriography or surgery. Digital ischemia was defined as a sudden decrease in limb perfusion characterized by an absence of arterial pulses, pale extremities, cyanosis or ischemic skin lesions, and absence of arterial blood flow on Doppler examination. ARDS was defined using the American-European Consensus Conference.[10]

We also recorded hemodynamic data, need for vasoactive drugs and other medications, need for mechanical ventilation, need for RRT and other forms of organ dysfunction. After discharge from the ICU, clinical outcomes were evaluated on the regular ward, still in a blinded fashion.

Primary outcome

In the design phase of the study, we selected Brussels criteria as the primary outcome because it was similar to a previous trial that compared vasopressin added to noradrenaline versus noradrenaline alone in septic shock patients.[11] On February 2013, before any study analysis had been undertaken, the trial leadership decided to modify the endpoint and had no knowledge of the endpoint or related trial data results.

The reason for this change was that few outcome data on vasoplegic patients were available in the literature, therefore the trial leadership considered appropriate to select the modified STS Score, which was demonstrated to better measure outcomes in the field of cardiac surgery.[12] In addition, there is a recognition that cardiac surgery setting differs from sepsis in that mortality in cardiac surgery is lower, and organ failure pattern and time course seem different.[13] By the moment this change was performed, a number of 81 patients were included in the study and the database had not been analyzed. An amendment was added to the study protocol and the ethics committee approved it. The original primary outcome data ("DAYS alive and free of organ dysfunction during the first 28 days according to the Brussels Criteria") are reported in the eTable 7.

RESULTS

- subgroup analysis

We performed a subgroup analysis of patients regarding the use of beta-blocker and ACEi/ARB in the last 7 days before surgery. At the Heart Institution, there is a perioperative care protocol recommending ACEi/ARBs withdrawal within 48 hours preoperative. To address potential imbalance of patient characteristics that would have occurred in spite of randomization, we performed a multivariable Cox proportional hazards model and the predictive variables of the primary outcome were chronic renal failure, initial hematocrit level and intraoperative use of epinephrine. We observed that the benefit of vasopressin in reducing the primary outcome is maintained regardless of the use of beta-blocker. Nevertheless, vasopressin did not reduce the primary outcome in the subgroup of patients not using ACEi/ARB (eTable 4).

References

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eTable 1. Classification/staging system for acute kidney injury.

Stage	Serum creatinine criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dL (≥ 26.4 μmol/L) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline
2	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline
3	Increase in serum creatinine to more than 300% (> 3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dL [≥ 354 μmol/L] with an acute increase of at least 0.5 mg/dL [44 μmol/L])

eTable 2. Intraoperative characteristics of study patients.

Variable	Norepinephrine (n=151)	Vasopressin (n=149)
Type of surgery		
CABG	73 (48.4%)	64 (43.0%)
Valve surgery	47 (31.1%)	55 (36.9%)
Combined cardiac surgery	31 (20.5%)	30 (20.1%)
Epinephrine	44 (29.1%)	39 (26.2%)
Dobutamine	55 (36.4%)	51 (34.2%)
RBC transfusion	31 (20.5%)	31 (20.8%)
Duration of CPB	80 (68 - 90)	79 (65 - 90)
Fluid balance (mean, SD)	2459 ± 802	2352 ± 824
Initial $ScvO_2$ (median, IQR)	67 (65 - 70)	65 (61 - 70)
Final $ScvO_2$ (median, IQR)	70 (63 - 75)	70 (66 - 75)
Initial Ht (median, IQR)	38 (36 - 40)	38 (36 - 40)
Final Ht (median, IQR)	30 (29 - 32)	30 (29 - 32)

SD – standard deviation; IQR – Interquartile range; CABG - Coronary artery bypass grafting; CPB - Cardiopulmonary bypass; $ScvO_2$ - central venous oxygen saturation; HT - hematocrit; Initial - beginning of surgery; Final - End of surgery.

eTable 3. Post-hoc outcomes in the two groups.

Variable	Norepinephrine (n=151)	Vasopressin (n=149)	Unadjusted Odds Ratio or Between-Group Difference (95%CI)	P	Adjusted* Odds Ratio or Between-Group Difference (95%CI)	p
Pulmonary thromboembolism	4 (2.6%)	4 (2.7%)	1.01 (0.25 - 4.13)	0.98	1.04 (0.25 - 4.32)	0.96
Low cardiac output	17 (11.3%)	13 (8.7%)	0.75 (0.35 - 1.61)	0.47	0.77 (0.36 - 1.65)	0.49
Delirium	27 (17.9%)	27 (18.1%)	1.02 (0.56 - 1.83)	0.96	0.97 (0.53 - 1.76)	0.92
AKIN						
0	56 (37.1%)	95 (65.5%)	Reference		Reference	
1	28 (18.5%)	29 (20.0%)	1.64 (0.89 - 3.03)	0.12	1.83 (0.94 - 3.54)	0.07
2	18 (11.9%)	9 (6.2%)	3.39 (1.43 - 8.06)	0.0057	5.49 (2.09 - 14.4)	0.0005
3	49 (32.5%)	12 (8.3%)	6.93 (3.4 - 14.12)	<0.0001	10.84 (4.54 - 25.88)	<0.0001
RRT	21 (13.9%)	4 (2.7%)	0.17 (0.06 - 0.51)	0.0016	0.11 (0.03 - 0.4)	0.0007
ARDS	20 (13.2%)	15 (10.1%)	0.73 (0.36 - 1.49)	0.39	0.76 (0.37 - 1.56)	0.45
Readmission	35 (23.2%)	29 (19.5%)	0.8 (0.46 - 1.39)	0.43	0.75 (0.39 - 1.47)	0.41
SOFA IPO, mean and SD	3·4 ± 1·5	3.1 ± 1.6	-0.32 (-0.67 to 0.03)	0.07	-0.31 (-0.63 to 0.01)	0.06
SOFA 1st POD, mean and SD	3·6 ± 2·3	2.8 ± 2.4	-0.82 (-1.35 to -0.29)	0.0025	-0.81 (-1.3 to -0.33)	0.0011
SOFA 2nd POD, mean and SD	3·7 ± 2·8	2.8 ± 3.1	-0.97 (-1.63 to -0.3)	0.0043	-0.97 (-1.57 to -0.37)	0.0014
SOFA 3rd POD, mean and SD	3·6 ± 3.0	2.4 ± 3.2	-1.21 (-1.91 to -0.5)	0.0008	-1.17 (-1.8 to -0.55)	0.0002
90-day mortality	26 (17.2%)	24 (16.1%)	0.92 (0.5 - 1.69)	0.80	0.91 (0.39 - 2.11)	0.82

AKIN - Acute kidney injury network; RRT – renal replacement therapy; SOFA - Sequential Organ Failure Assessment; IPO – Immediate postoperative period; POD – Postoperative day; ICU – Intensive care unit; IQR – Interquartile range.

* Adjustment was performed for predictive variables of the combined endpoint: chronic renal failure, initial hematocrit level and intraoperative use of epinephrine.

Odds ratio (OR) or between-group difference was used for secondary outcomes.

eTable 4. Effects of norepinephrine and vasopressin in the primary outcome, according to the use of beta-blocker or ACEI/ARB.

Variable	Norepinephrine	Vasopressin	Unadjusted hazard ratio	P	Adjusted hazard ratio	P
Beta-blocker use						
No (n=106)	31 (57.4%)	20 (38.5%)	0.539 (0.306 - 0.949)	0.032	0.439 (0.241 - 0.800)	0.007
Yes (n=194)	43 (44.3%)	28 (28.9%)	0.554 (0.343 - 0.894)	0.016	0.569 (0.352 - 0.921)	0.022
ACEI/ARB						
No (n=177)	34 (42.0%)	32 (33.3%)	0.695 (0.428 - 1.128)	0.141	0.659 (0.404 - 1.075)	0.095
Yes (n=123)	40 (57.1%)	16 (30.2%)	0.443 (0.247 - 0.795)	0.006	0.389 (0.214 - 0.706)	0.002

ACEI = angiotensin-conversion enzyme inhibitor; ARB = angiotensin receptor blocker.

Adjusted for chronic renal failure, initial hematocrit level and intraoperative use of epinephrine.

eTable 5. Vasopressor and hemodynamic data.

Variable	**Norepinephrine (n=151)**	**Vasopressin (n=149)**	***P* value†**	
Length of study drug infusion (h) median (IQR)	57 (22 - 114)	34 (13 - 75)	0·0003	*
Onset of drug infusion				
Operating room	50 (33.1%)	52 (34.9%)	0·69	**
IPO	77 (51.0%)	77 (51.7%)		
1st POD	20 (13.2%)	14 (9.4%)		
2nd POD	4 (2.6%)	6 (4.0%)		
Additional open-label norepinephrine	29 (19.2%)	17 (11.4%)	0·06	**
Length of dobutamine infusion (h). median (IQR)	54 (33 - 89)	40 (26 - 68)	0.01	*
Heart rate, median (IQR)				
Before drug infusion	120 (108 - 129)	120 (102 - 124)	0.15	*
15 min	118 (106 - 130)	118 (101 - 125)	0.26	*
30 min	117 (108 - 129)	117 (104 - 125)	0.21	*
60 min	117 (106 - 130)	116 (105 - 125)	0.22	*
12 h	114 (100 - 126)	113 (98 - 120)	0.26	*
24 h	110 (98 - 122)	108 (90 - 116)		*
MAP, median (IQR)				
Before drug infusion	55 (50 - 60)	58 (49 - 60)	0.90	*
15 min	63 (60 - 67)	65 (62 - 70)	0.028	*
30 min	68 (65 - 70)	69 (66 - 73)	0.25	*
60 min	70 (68 - 75)	72 (69 - 75)	0.06	*
12 h	73 (70 - 77)	74 (70 - 77)	0.08	*
Cardiac index, median (IQR)				
Before drug infusion	2·8 (2.6 - 3.0)	2.9 (2·6 - 3)	0.71	*
15 min	2·8 (2.6 - 3.0)	2.8 (2·6 - 3)	0.98	*
30 min	2·8 (2.5 - 3.0)	2.8 (2·6 - 3)	0.71	*
60 min	2·7 (2.6 - 3.0)	2.7 (2·6 - 2·9)	0.91	*
12 h	2·7 (2.5 - 2.9)	2.7 (2·5 - 2·8)	0.99	*
24 h	2·7 (2.5 - 2.9)	2.7 (2·5 - 2·9)	0.94	*
Fluid balance, median (IQR)				
IPO	650 (500 - 800)	700 (580 - 825)	0.88	*
1st POD	310 (260 - 450)	350 (270 - 475)	0.15	*
2nd POD	200 (150 - 330)	200 (150 - 300)	0.26	*

h – hours; min – minutes; IPO – Immediate postoperative period; POD – Postoperative day; IQR – Interquartile range. * Mann-Whitney U test; ** Chi square test, † comparison between groups

eTable 6. Laboratory data.

Variable, median (IQR)	Norepinephrine (n=151)	Vasopressin (n=149)	*P* value	
Hematocrit (%)				
IPO	28 (27 - 30)	28 (27 - 30)	0.75	*
1st POD	27 (26 - 29)	27 (26 - 28)	0.89	*
2nd POD	27 (26 - 28)	27 (26 - 28)	0.36	*
Creatinine (mg/dL)				
IPO	1.1 (0·9 - 1·6)	1.1 (0.9 - 1.3)	0.55	*
1st POD	1.5 (1·3 - 2·9)	1.4 (1.2 - 1.7)	0.003	*
2nd POD	1.8 (1·3 - 3·1)	1.3 (1.1 - 2.0)	<0.0001	*
3rd POD	2 (1·3 - 4·2)	1.4 (1.2 - 2.1)	<0.0001	*
CK-MB (ng/mL)				
IPO	21 (12 - 32)	21 (11 - 31)	0.60	*
1st POD	28 (17 - 41)	27 (18 - 34)	0.41	*
2nd POD	27 (21 - 39)	30 (19 - 36)	0.74	*
Troponin (ng/mL)				
IPO	2 (1 - 3.4)	2 (1.5 - 3.7)	0.66	*
1st POD	2.5 (2 - 4.3)	3 (2.1 - 4.4)	0.55	*
2nd POD	3.1 (2·5 - 5.1)	3.4 (2.5 - 4.3)	0.91	*
Lactate (mEq/L)				
Basal	5.3 (3·8 – 7.3)	5.1 (3.7 – 7.2)	0.39	*
6 hours	5.6 (4 ·5 – 7.6)	5.4 (4 – 7.2)	0.16	*
12 hours	3.7 (3·2 – 5.3)	3.5 (3.1 – 4.7)	0.06	*
24 hours	2.6 (1·8 – 3.7)	2.4 (2 – 3.2)	0.08	*
C-reactive protein (mg/L)				
IPO	67 (44 - 108)	92 (49 - 128)	0.06	*
1st POD	86 (58 - 109)	88 (66 - 131)	0.14	*
2nd POD	87 (56 - 117)	91 (65 - 121)	0.24	*
Platelet count (x10^3/□L)				
IPO	117 (98 - 141)	117 (91 - 142)	0.81	*
1st POD	122 (98 - 155)	117 (90 - 135)	0.13	*
2nd POD	111 (78 - 144)	107 (78 - 134)	0.44	*

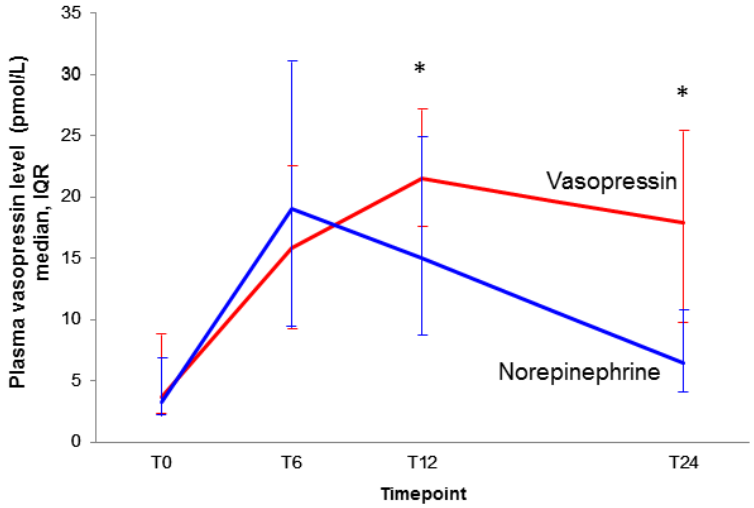
CK-MB – creatine kinase MB fraction; IPO – Immediate postoperative period; POD – Postoperative day; IQR – Interquartile range. * Mann-Whitney U test.

eTable 7. Original primary outcome.

Days alive / free of organ dysfunction	Norepinephrine	Vasopressin	P*
Cardiovascular	25 (21 - 27)	26 (24 - 27)	0.018
Respiratory	27 (27 - 27)	27 (27 - 27)	0.642
Renal	19 (8 - 28)	28 (20 - 28)	<0.001
Hepatic	28 (28 - 28)	28 (28 - 28)	0.918
Hematologic	25 (19 - 28)	26 (23 - 28)	0.132
Neurologic	28 (28 - 28)	28 (28 - 28)	0.918

*Mann-Whitney test

Median and interquartile range



eFigure 1. Plasma vasopressin levels over time in 89 patients. *significant difference vasopressin versus norepinephrine group at T12 ($p=0.027$) and T24 ($p<0.001$).