Comparison of Dopamine and Norepinephrine in the Treatment of Shock

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Background

- Circulatory shock is a life-threatening condition that associate with high mortality
- Fluid challenge, the 1st-line therapeutic strategy, is often insufficient to stabilize the patient's condition
- Adrenergic agents are frequently required to correct hypotension
- Dopamine and Norepinephrine are used most frequently

Background

- Both of them influence α- adrenergic and β-adrenergic receptors, but to different degrees
- α-adrenergic effects ↑ vascular tone but may ↓ cardiac output and ↓ regional blood flow, especially in cutaneous, splanchnic, and renal beds
- β-adrenergic effects help to maintain blood flow through inotropic and chronotropic effects and to ↑ splanchnic perfusion
- β-adrenergic stimulation can also ↑ cellular metabolism and immunosuppression

Background

- Dopamine also stimulates dopaminergic receptors, result a proportionately greater ↑ splanchnic & renal perfusion, it may facilitate resolution of lung edema
- However, dopaminergic stimulation can have harmful immunologic effects by altering hypothalamo–pituitary function, resulting in a marked ↓ prolactin & growth hormone levels

Background

- Thus, Dopamine and Norepinephrine may have different effects on the kidney, splanchnic region, and pituitary axis
- Consensus guidelines and expert recommendations suggest that either agent may be used as a 1st-choice vasopressor in patients with shock
- This study was designed to evaluate whether the choice of Norepinephrine over Dopamine as the 1st-line vasopressor agent could reduce the rate of death among patients in shock

Method

- Multicenter, randomized, blinded trial
- ≧18 y/o , 12/19/2003 ~ 10/6/2007
- In 8 centers in Belgium, Austria, and Spain
- MAP < 70mmHg or SBP < 100mmHg after adequate fluids (at least 1000mL crystalloid or 500mL colloid)
- (unless CVP >12mmHg or in pulmonary artery occlusion pressure to >14mmHg)
- Signs of tissue hypoperfusion (e.g., altered mental state, mottled skin, urine output <0.5 mL/Kg/hr, or serum lactate level >2 mmol/L)

Method

Exclusion:

- < 18y/o
- Had already received a vasopressor agent (Dopamine, Norepinephrine, Epinephrine, or Phenylephrine) for >4 hours during the current episode of shock
- Had a serious arrhythmia, such as rapid Af (>160bpm) or VT
- Had been declared brain-dead

Protocol

- dose was determined according to the patient's body weight
- Dopamine could be increased or decreased by 2 μg/Kg/min
- Norepinephrine by 0.02 μg/Kg/min

Protocol

- If still hypotension after maximum dose (20 μg/Kg/min for Dopamine or 0.19 μg/Kg/min for Norepinephrine), open-label Norepinephrine was added
- Epinephrine and vasopressin were used only as rescue therapy
- Inotropic agents could be used, if needed, to increase cardiac output

Protocol

- The study period lasted a maximum of 28 days
- The study drug was reinstituted, if necessary, in patients who were discharged from the ICU but were readmitted within 28 days after randomization, allowing maximal exposure to the study drug
- After day 28, the choice of vasopressor agent was left to the discretion of the physician in charge

Protocol

- If adverse events occurred during treatment with the study drug, the physician in charge could withdraw the patient from the study and switch him or her to open-label vasopressor therapy

End points

Primary: rate of death at 28 days

Secondary:

- rates of death in the ICU, in the hospital, at 6 months, and at 12 months;
- the duration of stay in the ICU;
- the number of days without need for organ support (i.e., vasopressors, ventilators, or renal-replacement therapy);
- the time to attainment of hemodynamic stability (i.e., time to reach a MAP 65mmHg);
- the changes in hemodynamic variables;
- the use of Dobutamine or other inotropic agents

End points

- Adverse events were categorized as arrhythmias (i.e., VT, VF, or Af), myocardial necrosis, skin necrosis, ischemia in limbs, or secondary infections

Measured Variables

The following data were recorded every 6 hours for 48 hours, every 8 hours on days 3, 4, and 5, and once a day on days 6, 7, 14, 21, and 28

- Vital signs
- hemodynamic variables (including systolic and diastolic arterial pressures, HR, CVP, and, if possible, pulmonary-artery pressures)
- cardiac output
- ABG and VBG
- doses of vasoactive agents
- respiratory conditions

Measured Variables

- Biologic variables, data on daily fluid balance, microbiologic data, and antibiotic therapy were recorded daily for the first 7 days and then on days 14, 21, and 28
- The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated at the time of admission to the ICU and at the time of enrollment in the study
- The Sequential Organ Failure Assessment (SOFA) score was calculated daily for the first 7 days and then on days 14, 21, and 28

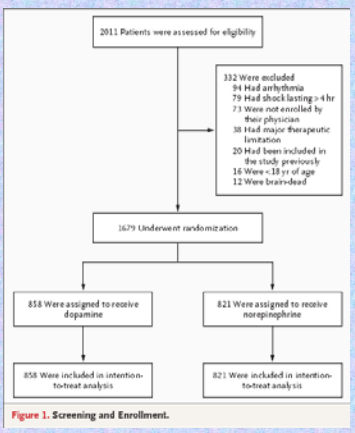

Figure 1. Screening and Enrollment.

Table 1. Baseline Characteristics of the Patients and Major Therapeutic Interventions at Baseline.*

Variable	Dopamine (N=858)	Norepinephrine (N=821)
Age — yr		
Median	68	67
Interquartile range	55–76	56–76
Male sex — no. (%)	507 (59.1)	449 (54.7)
APACHE II score†		
Median	20	20
Interquartile range	15–28	14–27
SOFA score‡		
Median	9	9
Interquartile range	7–12	6–12
Reason for admission — no. (%)		
Medical	565 (65.9)	532 (64.8)
Scheduled surgery	168 (19.6)	161 (19.6)
Emergency surgery	125 (14.6)	128 (15.6)
Cause of shock — no. (%)		
Sepsis	542 (63.2)	502 (61.1)
Lungs	278 (32.4)	246 (30.0)
Abdomen	138 (16.1)	135 (16.4)
Urine	51 (5.9)	42 (5.1)
Catheter	14 (1.6)	10 (1.2)
Endocardium	9 (1.0)	11 (1.3)
Mediastinum	10 (1.2)	15 (1.8)
Soft tissues	11 (1.3)	13 (1.6)
Other	15 (1.7)	20 (2.4)
Cardiogenic source	135 (15.7)	145 (17.6)
Myocardial infarction	75 (8.7)	86 (10.5)
Dilated cardiomyopathy	25 (2.9)	19 (2.3)
Tamponade	2 (0.2)	7 (0.9)
Pulmonary embolism	10 (1.2)	8 (1.0)
Valvular disease	4 (0.5)	5 (0.6)
After cardiopulmonary bypass	19 (2.2)	20 (2.4)
Other		
Hypovolemia	138 (16.1)	125 (15.2)
Hemorrhage	130 (15.2)	116 (14.1)
Trauma	17 (2.0)	23 (2.8)
Gastrointestinal bleeding	31 (3.6)	22 (2.7)
Bleeding at surgical site	64 (7.5)	57 (6.9)
Other	18 (2.1)	14 (1.7)
Dehydration	8 (0.9)	9 (1.1)
Other	48 (5.9)	44 (5.0)
Spinal	6 (0.7)	8 (1.0)
Peridural§	13 (1.5)	4 (0.5)
Intoxication-related¶	7 (0.8)	4 (0.5)
Anaphylactic	3 (0.3)	4 (0.5)
Miscellaneous	13 (1.5)	29 (3.5)
Hemodynamic, respiratory, and biologic variables		
Temperature — °C	36.6±1.5	36.6±1.5
Heart rate — beats/min	97±27	95±25‖
Mean arterial pressure — mm Hg	58±13	58±13
Mean pulmonary-artery pressure — mm Hg**	27±9	29±8‖

Variable	Dopamine (N=858)	Norepinephrine (N=821)
Pulmonary-artery occlusion pressure — mm Hg**	16±6	18±6]
Central venous pressure — mm Hg††	13±6	13±5
Cardiac index — liters/min/m²‡‡	3.11±1.35	2.77±1.16]
Arterial pH	7.32±0.13	7.32±0.14
$PaCO_2$ — mm Hg	42±16	41±14
PaO_2 — mm Hg	110±75	123±84]]
SaO_2 — %	95±5	96±4]]
SvO_2 — %¶¶	64±9	62±13
Lactate — mmol/liter		
Median	2.1	2.2
Interquartile range	1.2–4.3	1.2–3.8
Hemoglobin — g/dl	9.8±2.5	9.9±2.5
Creatinine — mg/dl		
Median	1.4	1.3
Interquartile range	0.8–2.4	0.8–2.3
Respiratory rate — per min	21±8	21±8
Ratio of PaO_2 to FiO_2	210±157	234±165]]
Major therapeutic interventions		
Mechanical ventilation — no. (%)	615 (71.7)	580 (70.6)
Tidal volume — ml/kg of ideal body weight	8.0±1.9	7.9±1.9
Positive end-expiratory pressure — cm of water	6±3	6±2
FiO_2	0.59±0.24	0.58±0.23
Renal-replacement therapy — no. (%)	63 (7.3)	61 (7.4)
Open-label norepinephrine		
Patients treated — no. (%)	157 (18.3)	107 (13.0)]]
Dose — μg/kg/min	0.58±0.80	0.54±0.87
Epinephrine		
Patients treated — no. (%)	13 (1.5)	9 (1.1)
Dose — μg/kg/min	1.1±2.8	1.3±1.9
Dobutamine		
Patients treated — no. (%)	127 (14.8)	159 (19.4)]
Dose — μg/kg/min	10±6	9±6
Vasopressin		
Patients treated — no. (%)	2 (0.2)	2 (0.2)
Dose — U/min	0.03	0.03
Corticosteroids — no. (%)‡‡	101 (11.8)	74 (9.3)

Table 2. Mortality Rates.*

Time Period	Dopamine	Norepinephrine	Odds Ratio (95% CI)†	P Value
	percent mortality			
During stay in intensive care unit	50.2	45.9	1.19 (0.98–1.44)	0.07
During hospital stay	59.4	56.6	1.12 (0.92–1.37)	0.24
At 28 days	52.5	48.5	1.17 (0.97–1.42)	0.10
At 6 mo	63.8	62.9	1.06 (0.86–1.31)	0.71
At 12 mo	65.9	63.0	1.15 (0.91–1.46)	0.34

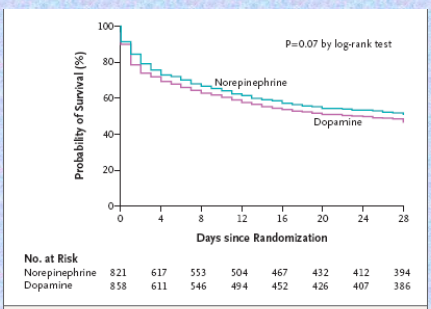

Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.

Table 3. Secondary Outcomes and Adverse Events.*

Variable	Dopamine (N=858)	Norepinephrine (N=821)	P Value
Support-free days through day 28			
Vasopressors not needed			
Trial drug	11.0±12.1	12.5±12.1	0.01
Open-label vasopressors	12.6±12.5	14.2±12.3	0.007
Mechanical ventilation not needed	8.5±11.2	9.5±11.4	0.13
Renal support not needed	12.8±12.4	14.0±12.3	0.07
Intensive care not needed	8.1±10.3	8.5±10.3	0.43
Length of stay — no. of days			
Intensive care unit			0.12
Median	5	5	
Interquartile range	1–11	2–12	
Hospital			0.22
Median	11	12	
Interquartile range	2–28	3–28	
Cause of death in hospital — no./total no. (%)			0.31
Refractory shock	196/426 (46)	155/381 (41)	
Withdrawal or withholding of therapy	193/426 (45)	190/381 (50)	
Brain death or severe postanoxic lesions	37/426 (9)	36/381 (9)	

Adverse events			
Arrhythmias — no. (%)	207 (24.1)	102 (12.4)	<0.001
Atrial fibrillation	176 (20.5)	90 (11.0)	
Ventricular tachycardia	21 (2.4)	8 (1.0)	
Ventricular fibrillation	10 (1.2)	4 (0.5)	
Myocardial infarction — no. (%)	19 (2.2)	25 (3.0)	0.29
New infectious episode			
No. of episodes			0.69
Median	1	1	
Interquartile range	0–1	0–1	
Patients with at least one episode — no. (%)	674 (78.6)	619 (75.4)	0.35
Skin ischemia — no. (%)	56 (6.5)	34 (4.1)	0.09
Mild†	46 (5.4)	28 (3.4)	
Severe‡	10 (1.2)	6 (0.7)	
Arterial occlusion — no. (%)§	23 (2.7)	20 (2.4)	0.12
Arms or fingers	5 (0.6)	1 (0.1)	
Legs	7 (0.8)	13 (1.6)	
Bowel	11 (1.3)	6 (0.7)	

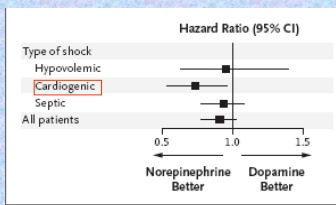

Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.

A total of 1044 patients were in septic shock (542 in the dopamine group and 502 in the norepinephrine group), 280 were in cardiogenic shock (135 in the dopamine group and 145 in the norepinephrine group), and 263 were in hypovolemic shock (138 in the dopamine group and 125 in the norepinephrine group). The P value for interaction was 0.87.

Discussion

- No significant difference in the rate of death at 28 days
- Dopamine was associated with more arrhythmic events
- Arrhythmic events that were severe enough to require withdrawal from the study were more frequent in the dopamine group
- Dopamine was associated with a significant increase in the rate of death in the predefined subgroup of patients with cardiogenic shock

Discussion

- These data strongly challenge the current American College of Cardiology–American Heart Association (ACC-AHA) guidelines, which recommend dopamine as the first-choice agent to increase arterial pressure among patients who have hypotension as a result of an acute myocardial infarction

Thank you for your attention!