The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 4, 2010 VOL. 362 NO. 9

Comparison of Dopamine and Norepinephrine in the Treatment of Shock

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ABSTRACT

BACKGROUND

Both dopamine and norepinephrine are recommended as first-line vasopressor agents in the treatment of shock. There is a continuing controversy about whether one agent is superior to the other.

METHODS

In this multicenter, randomized trial, we assigned patients with shock to receive either dopamine or norepinephrine as first-line vasopressor therapy to restore and maintain blood pressure. When blood pressure could not be maintained with a dose of 20 μg per kilogram of body weight per minute for dopamine or a dose of 0.19 μg per kilogram per minute for norepinephrine, open-label norepinephrine, epinephrine, or vasopressin could be added. The primary outcome was the rate of death at 28 days after randomization; secondary end points included the number of days without need for organ support and the occurrence of adverse events.

RESULTS

The trial included 1679 patients, of whom 858 were assigned to dopamine and 821 to norepinephrine. The baseline characteristics of the groups were similar. There was no significant between-group difference in the rate of death at 28 days (52.5% in the dopamine group and 48.5% in the norepinephrine group; odds ratio with dopamine, 1.17; 95% confidence interval, 0.97 to 1.42; P=0.10). However, there were more arrhythmic events among the patients treated with dopamine than among those treated with norepinephrine (207 events [24.1%] vs. 102 events [12.4%], P<0.001). A subgroup analysis showed that dopamine, as compared with norepinephrine, was associated with an increased rate of death at 28 days among the 280 patients with cardiogenic shock but not among the 1044 patients with septic shock or the 263 with hypovolemic shock (P=0.03 for cardiogenic shock, P=0.19 for septic shock, and P=0.84 for hypovolemic shock, in Kaplan–Meier analyses).

CONCLUSIONS

Although there was no significant difference in the rate of death between patients with shock who were treated with dopamine as the first-line vasopressor agent and those who were treated with norepinephrine, the use of dopamine was associated with a greater number of adverse events. (ClinicalTrials.gov number, NCT00314704.)

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N Engl J Med 2010;362:779-89.

Circulatory shock is a life-threatening condition that is associated with high mortality.[1,2] The administration of fluids, which is the first-line therapeutic strategy, is often insufficient to stabilize the patient's condition, and adrenergic agents are frequently required to correct hypotension. Among these agents, dopamine and norepinephrine are used most frequently.[3] Both of these agents influence alpha-adrenergic and beta-adrenergic receptors, but to different degrees. Alpha-adrenergic effects increase vascular tone but may decrease cardiac output and regional blood flow, especially in cutaneous, splanchnic, and renal beds. Beta-adrenergic effects help to maintain blood flow through inotropic and chronotropic effects and to increase splanchnic perfusion. This beta-adrenergic stimulation can have unwanted consequences as well, including increased cellular metabolism and immunosuppressive effects. Dopamine also stimulates dopaminergic receptors, resulting in a proportionately greater increase in splanchnic and renal perfusion, and it may facilitate resolution of lung edema.[4] However, dopaminergic stimulation can have harmful immunologic effects by altering hypothalamo–pituitary function, resulting in a marked decrease in prolactin and growth hormone levels.[5]

Thus, dopamine and norepinephrine may have different effects on the kidney, the splanchnic region, and the pituitary axis, but the clinical implications of these differences are still uncertain. Consensus guidelines and expert recommendations suggest that either agent may be used as a first-choice vasopressor in patients with shock.[6-8] However, observational studies have shown that the administration of dopamine may be associated with rates of death that are higher than those associated with the administration of norepinephrine.[3,9,10] The Sepsis Occurrence in Acutely Ill Patients (SOAP) study,[3] which involved 1058 patients who were in shock, showed that administration of dopamine was an independent risk factor for death in the intensive care unit (ICU). In a meta-analysis,[11] only three randomized studies, with a total of just 62 patients, were identified that compared the effects of dopamine and norepinephrine in patients with septic shock. The lack of data from clinical trials in the face of growing observational evidence that norepinephrine may be associated with better outcomes called for a randomized, controlled trial. Our study was designed to evaluate whether the choice of norepinephrine over dopamine as the first-line vasopressor agent could reduce the rate of death among patients in shock.

Methods

Study Patients

We conducted this multicenter trial between December 19, 2003, and October 6, 2007, in eight centers in Belgium, Austria, and Spain. All patients 18 years of age or older in whom a vasopressor agent was required for the treatment of shock were included in the study. The patient was considered to be in shock if the mean arterial pressure was less than 70 mm Hg or the systolic blood pressure was less than 100 mm Hg despite the fact that an adequate amount of fluids (at least 1000 ml of crystalloids or 500 ml of colloids) had been administered (unless there was an elevation in the central venous pressure to >12 mm Hg or in pulmonary-artery occlusion pressure to >14 mm Hg) and if there were signs of tissue hypoperfusion (e.g., altered mental state, mottled skin, urine output of <0.5 ml per kilogram of body weight for 1 hour, or a serum lactate level of >2 mmol per liter). Patients were excluded if they were younger than 18 years of age; had already received a vasopressor agent (dopamine, norepinephrine, epinephrine, or phenylephrine) for more than 4 hours during the current episode of shock; had a serious arrhythmia, such as rapid atrial fibrillation (>160 beats per minute) or ventricular tachycardia; or had been declared brain-dead.

Protocol

Randomization was performed in computer-generated, permuted blocks of 6 to 10, stratified according to the participating ICU. Treatment assignments and a five-digit reference number were placed in sealed, opaque envelopes, which were opened by the person responsible for the preparation of the trial-drug solutions. The solutions of norepinephrine or dopamine were prepared in vials or syringes according to the preference of the local ICU. Each vial or syringe was then labeled with its randomly allocated number. The doctors and nurses administering the drugs, as well as the local investigators and research personnel who collected data, were unaware of the treatment assignments. The trial was approved by the ethics committee at each participating center. Written informed consent was obtained from all patients or next of kin.

The dose was determined according to the patient's body weight. Doses of dopamine could be increased or decreased by 2 μg per kilogram per minute and doses of norepinephrine by 0.02 μg per kilogram per minute (or more in emergency cases) (see Fig. 1 and 2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). An example of the dose-escalation table is provided in Table 1 in the Supplementary Appendix. The target blood pressure was determined by the doctor in charge for each individual patient. If the patient was still hypotensive after the maximum dose of either agent had been administered (20 μg per kilogram per minute for dopamine or 0.19 μg per kilogram per minute for norepinephrine — doses that have been shown to have similar effects on mean arterial blood pressure[12,13]), open-label norepinephrine was added. The dose of 20 μg per kilogram per minute for dopamine was selected as the maximal dose because this upper limit was the standard of care in the participating ICUs, in line with expert recommendations[14] and international guidelines.[15]

If the patient was already being treated with a vasopressor at baseline, that agent was replaced as soon as possible with the trial-drug solution. If the patient was already receiving dopamine and this agent could not be discontinued after introduction of the trial-drug solution, the dopamine was replaced with an open-label norepinephrine infusion. Open-label dopamine was not allowed at any time. Epinephrine and vasopressin were used only as rescue therapy. Inotropic agents could be used, if needed, to increase cardiac output.

When the patients were weaned from vasopressor agents, any open-label norepinephrine that was being administered was withdrawn first, after which the trial-drug solution was withdrawn. If hypotension recurred, the trial-drug solution was resumed first (at the same maximal dose) and an open-label solution of norepinephrine was added if needed.

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.

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. All other treatment decisions were left to the discretion of the attending physicians.

END POINTS

The primary end point of the trial was the rate of death at 28 days. Secondary end points were the 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 mean arterial pressure of 65 mm Hg)[16]; the changes in hemodynamic variables; and the use of dobutamine or other inotropic agents. Adverse events were categorized as arrhythmias (i.e., ventricular tachycardia, ventricular fibrillation, or atrial fibrillation), myocardial necrosis, skin necrosis, ischemia in limbs or distal extremities, or secondary infections.[17]

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, heart rate, central venous pressure, and, when possible, pulmonary-artery pressures), cardiac output, arterial and mixed-venous (or central venous) blood gas levels, doses of vasoactive agents, and respiratory conditions. 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[18] was calculated at the time of admission to the ICU and at the time of enrollment in the study, and the Sequential Organ Failure Assessment (SOFA) score[19] was calculated daily for the first 7 days and then on days 14, 21, and 28.

STATISTICAL ANALYSIS

On the basis of the results of the SOAP study,[3] which showed a rate of death of 43% among patients receiving dopamine and a rate of 36% among patients receiving norepinephrine, we estimated that with 765 patients in each group, the study would have 80% power to show a 15% relative dif-

ference in the rate of death at 28 days, at a two-sided alpha level of 0.05.

Since the magnitude of the effect derived from observational studies can be misleading, we opted for a sequential trial design with two-sided alternatives[20]; the trial design called for analyses to be performed after inclusion of the first 50 and 100 patients, and then after inclusion of each additional 100 patients, and allowed for the discontinuation of the trial according to the following predefined boundaries: superiority of norepinephrine over dopamine, superiority of dopamine over norepinephrine, or no difference between the two. An independent statistician who is also a physician monitored the efficacy analyses and the adverse events; on October 6, 2007, after analysis of the outcome in the first 1600 patients showed that one of the three predefined boundaries had been crossed, the statistician advised that the trial be stopped.

All data were analyzed according to the intention-to-treat principle. Differences in the primary outcome were analyzed with the use of an unadjusted chi-square test. Results are presented as absolute and relative risks and 95% confidence intervals. Kaplan–Meier curves for estimated survival were compared with the use of a log-rank test. A Cox proportional-hazards regression model was used to evaluate the influence of potential confounding factors on the outcome (factors were selected if the P value in the univariate analysis was <0.20).

A predefined subgroup analysis of the primary outcome was conducted according to the type of shock (septic, cardiogenic, or hypovolemic). A test for interaction was performed, and the results are presented in a forest plot.

Other binary end points were analyzed with the use of chi-square tests, and continuous variables were compared by means of an unpaired Student's t-test or a Wilcoxon rank-sum test, as appropriate, with the use of SPSS software, version 13.0 (SPSS). All reported P values are two-sided and have not been adjusted for multiple testing. The study statistician and investigators remained unaware of the patients' treatment assignments while they performed the final analyses.

RESULTS

PATIENTS

A total of 1679 patients were enrolled — 858 in the dopamine group and 821 in the norepinephrine group (Fig. 1). All patients were followed to day 28; data on the outcome during the stay in the hospital were available for 1656 patients (98.6%), data on the 6-month outcome for 1443 patients (85.9%), and data on the 12-month outcome for 1036 patients (61.7%). There were no significant differences between the two groups with regard to most of the baseline characteristics (Table 1); there were small differences, which were of questionable clinical relevance, in the heart rate, partial pressure of arterial carbon dioxide ($PaCO_2$), arterial oxygen saturation (SaO_2), and ratio of partial pressure of arterial oxygen (PaO_2) to fraction of inspired oxygen (FIO_2). The type of shock that was seen most frequently was septic shock (in 1044 patients [62.2%]), followed by cardiogenic shock (in 280 patients [16.7%]) and hypovolemic shock (in 263 patients [15.7%]). The sources of sepsis are detailed in Table 2 in the Supplementary Appendix. Hydrocortisone was administered in 344 patients who received dopamine (40.1%) and in 326 patients who received norepinephrine (39.7%). Among patients with septic shock, recombinant activated human protein C was administered in 102 patients in the dopamine group (18.8%) and 96 patients in the norepinephrine group (19.1%).

Data on hemodynamic variables and doses of vasoactive agents are shown in Figure 3 and Figure 4 in the Supplementary Appendix. The mean arterial pressure was similar in the two treatment groups at baseline, and it changed similarly over time, although it was slightly higher from 12 to 24 hours in the norepinephrine group. The doses of the study drug were similar in the two groups at all times. More patients in the dopamine group than in the norepinephrine group required open-label norepinephrine therapy at some point (26% vs. 20%, P<0.001), but the doses of open-label norepinephrine that were administered were similar in the two groups. The use of open-label epinephrine at any time was similar in the two groups (administered in 3.5% of patients in the dopamine group and in 2.3% of those in the norepinephrine group, P=0.10), as was the use of vasopressin (0.2% in both groups, P=0.67). Dobutamine was used more frequently in patients treated with norepinephrine, but 12 hours after randomization, the doses of dobutamine were significantly higher in patients treated with dopamine. The mean (±SD) time to the achievement of a mean arterial pressure of 65 mm Hg was similar in the two groups (6.3±5.6 hours in the dopamine group and 6.0±4.9 hours in the norepinephrine group,

P=0.35). There were no major between-group differences in the total amounts of fluid given, although patients in the dopamine group received more fluids on day 1 than did patients in the norepinephrine group. Urine output was significantly higher during the first 24 hours after randomization among patients in the dopamine group than among those in the norepinephrine group, but this difference eventually disappeared, so that the fluid balance was quite similar between the two groups.

The increase in heart rate was greater in patients treated with dopamine than in patients treated with norepinephrine, up to 36 hours after randomization; the changes in the cardiac index, central venous pressure, venous oxygen saturation, and lactate levels were similar in the two groups.

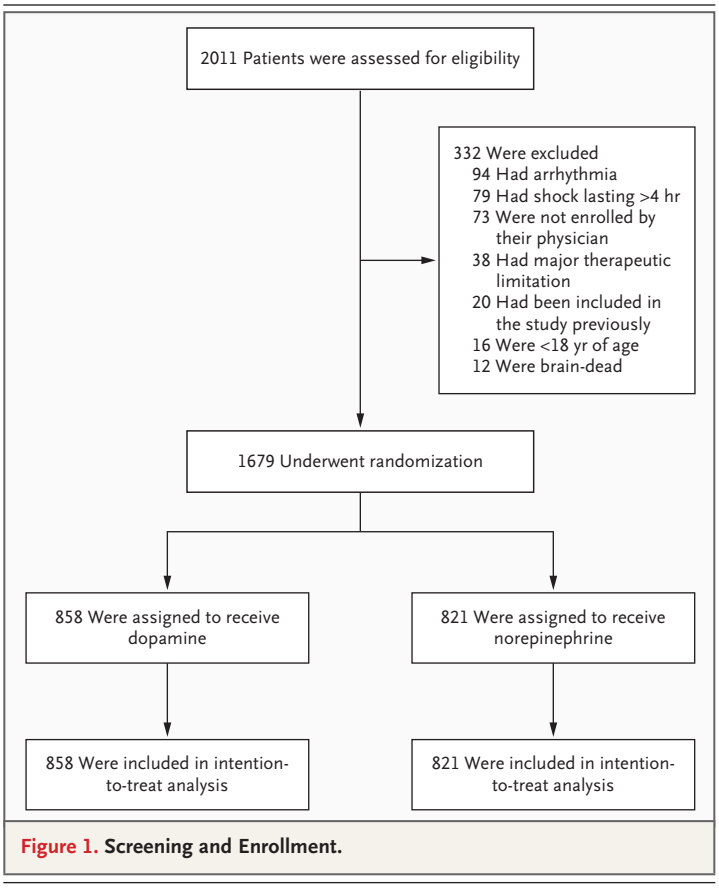

Figure 1. Screening and Enrollment.

OUTCOME

The boundary for stopping the trial owing to the lack of evidence of a difference between treatments at a P value of 0.05 was crossed (Fig. 5 in the Supplementary Appendix). There were no significant differences between the groups in the rate of death at 28 days or in the rates of death in the ICU, in the hospital, at 6 months, or at 12 months (Table 2). Kaplan–Meier curves for estimated survival showed no significant differences in the outcome (Fig. 2). Cox proportional-hazards analyses that included the APACHE II score, sex, and other relevant variables yielded similar results (Fig. 6 in the Supplementary Appendix). There were more days without need for the trial drug and more days without need for open-label vasopressors in the norepinephrine group than in the dopamine group, but there were no significant differences between the groups in the number of days without need for ICU care and in the number of days without need for organ support (Table 3). There were no significant differences in the causes of death between the two groups, although death from refractory shock occurred more frequently in the group of patients treated with dopamine than in the group treated with norepinephrine (P=0.05).

ADVERSE EVENTS

Overall, 309 patients (18.4%) had an arrhythmia; the most common type of arrhythmia was atrial fibrillation, which occurred in 266 patients (86.1%). More patients had an arrhythmia, especially atrial fibrillation, in the dopamine group than in the norepinephrine group (Table 3). The study drug was discontinued in 65 patients owing to severe arrhythmias — 52 patients (6.1%) in the dopamine group and 13 patients (1.6%) in the norepinephrine group (P<0.001). These patients were included in the intention-to-treat analysis. There were no significant differences between the groups in the incidences of other adverse events.

ADDITIONAL ANALYSES

A predefined subgroup analysis was conducted according to the type of shock — septic shock, which occurred in 1044 patients (542 in the dopamine group and 502 in the norepinephrine group); cardiogenic shock, which occurred in 280 patients (135 in the dopamine group and 145 in the norepinephrine group); or hypovolemic shock, which occurred in 263 patients (138 in the dopamine group and 125 in the norepinephrine group). The overall effect of treatment did not differ significantly among these subgroups (P=0.87 for interaction), although the rate of death at 28 days was significantly higher among patients with cardiogenic shock who were treated with dopamine than among those with cardiogenic shock who were treated with norepinephrine (P=0.03) (Fig. 3). The

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‖

Table 1. (Continued.)

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	236±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)	76 (9.3)

* Plus–minus values are means ±SD. To convert the values for creatinine to micromoles per liter, multiply by 88.4. FIO_2 denotes fraction of inspired oxygen, $PaCO_2$ partial pressure of arterial carbon dioxide, PaO_2 partial pressure of arterial oxygen, SaO_2 arterial oxygen saturation, and SvO_2 venous oxygen saturation.

† Scores on the Acute Physiologic and Chronic Health Evaluation II (APACHE II) scale range from 0 to 71, with higher values indicating more severe disease.[18]

‡ Scores on the Sequential Organ Failure Assessment (SOFA) scale range from 0 to 4 for each organ system, with higher scores indicating more severe organ dysfunction.[19]

§ Peridural shock refers to vasodilatory shock induced by peridural or epidural infusion in otherwise uncomplicated procedures.

¶ The 11 cases of intoxication were drug overdoses (5 cases) and voluntary intoxication with benzodiazepines (3), tricyclic antidepressants (2), and calcium-channel blockers (1).

‖ P<0.05 for the comparison of norepinephrine with dopamine.

** Data were available for 277 patients.

†† Data were available for 1249 patients.

‡‡ Data were available for 336 patients.

§§ P<0.01 for the comparison of norepinephrine with dopamine.

¶¶ Data were available for 357 patients.

‖‖ Corticosteroids administered at baseline included hydrocortisone and prednisolone.

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

* Data were available for 1656 patients in the intensive care unit, in the hospital, and at 28 days; for 1443 patients at 6 months; and for 1036 patients at 12 months.
† Odds ratios for death are for the comparison of the dopamine group with the norepinephrine group.

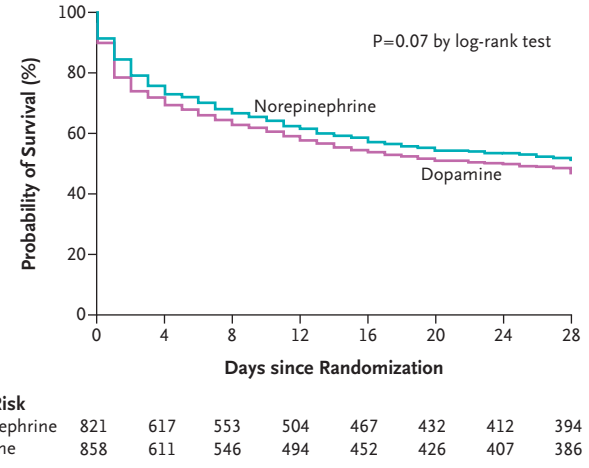

Figure 2. Kaplan–Meier Curves for 28-Day Survival in the Intention-to-Treat Population.

Kaplan–Meier curves for the subgroup analysis according to type of shock are shown in Figure 7 in the Supplementary Appendix.

DISCUSSION

In this multicenter, randomized, blinded trial comparing dopamine and norepinephrine as the initial vasopressor therapy in the treatment of shock, there was no significant difference in the rate of death at 28 days between patients who received dopamine and those who received norepinephrine. Dopamine was associated with more arrhythmic events than was norepinephrine, and arrhythmic events that were severe enough to require withdrawal from the study were more frequent in the dopamine group. In addition, dopamine was associated with a significant increase in the rate of death in the predefined subgroup of patients with cardiogenic shock.

The rate of death at 28 days in this study was close to 50%, which is to be expected in a study with very few exclusion criteria and is similar to the rate in previous observational studies.[3,9,21-24] Our trial was a pragmatic study that included all patients who were treated for shock states, and therefore, it has high external validity. The study design allowed for maximal exposure to the study drug, since we included patients who had received open-label vasopressors for a maximum of 4 hours before randomization and since during the 28-day study period, the study drug was withdrawn last when patients were weaned from vasopressor therapies and was resumed first if resumption of vasopressor therapy was necessary.

Smaller observational studies have suggested that treatment with dopamine may be detrimental to patients with septic shock.[3,9,10] However, Póvoa et al. reported a lower rate of death among patients treated with dopamine than among those treated with norepinephrine.[25] In our study, which included more than 1000 patients with septic shock, there was no significant difference in the outcome between patients treated with dopamine and those treated with norepinephrine.

Among patients with cardiogenic shock, the rate of death was significantly higher in the group treated with dopamine than in the group treated with norepinephrine, although one might expect that cardiac output would be better maintained with dopamine[26-28] than with norepinephrine. The exact cause of the increased mortality cannot be

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)	

* Plus–minus values are means ±SD.
† Mild skin ischemia was defined as a cold and cyanotic skin area, with capillary refill time of more than 2 seconds.
‡ Severe skin ischemia was defined as cold and black skin, with no bleeding on puncture.
§ Arterial occlusion in an extremity was considered to be present if an extremity was cold, if the capillary refill time was prolonged (>2 seconds), and if there was no pulse in the nutritive artery. Vascular occlusion in the bowel was considered to be present if bowel ischemia was detected by laparotomy, computed tomography, or colonoscopy.

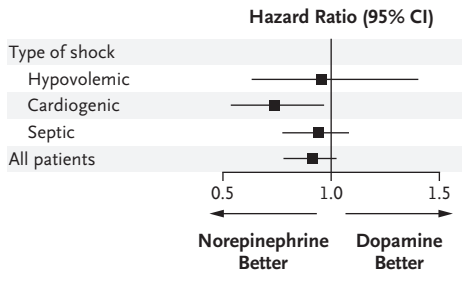

Figure 3. Forest Plot for Predefined Subgroup Analysis According to Type of Shock.

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.

determined, but the early difference in the rate of death suggests that the higher heart rate with dopamine may have contributed to the occurrence of ischemic events. Whatever the mechanism may be, these data strongly challenge the current American College of Cardiology–American Heart Association 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.[7]

This study has several limitations. First, dopamine is a less potent vasopressor than norepinephrine; however, we used infusion rates that were roughly equipotent with respect to systemic arterial pressure, and there were only minor differences in the use of open-label norepinephrine, most of which were related to early termination of the study drug and a shift to open-label norepinephrine because of the occurrence of arrhythmias that were difficult to control. Doses of open-label norepinephrine and the use of open-label epinephrine and vasopressin were similar between the two groups. Second, we used a sequential design, which potentially allowed us to stop the study early if an effect larger than that expected from observational trials occurred; however, the trial was eventually stopped after inclusion of more patients than we had expected to be included on the basis of our estimates of the sample size. Accordingly, all conclusions related to the primary outcome reached the predefined power.

In summary, although the rate of death did not differ significantly between the group of patients treated with dopamine and the group treated with norepinephrine, this study raises serious concerns about the safety of dopamine therapy, since dopamine, as compared with norepinephrine, was associated with more arrhythmias and with an increased rate of death in the subgroup of patients with cardiogenic shock.

Supported in part by the European Society of Intensive Care through support from the European Critical Care Research Network

Dr. Aldecoa reports receiving consulting fees from Covidien. No other potential conflict of interest relevant to this article was reported.

APPENDIX

Other investigators and participants in the trial are as follows: R. Kitzberger, U. Holzinger, Medical University of Vienna, Vienna; A. Roman, Centre Hospitalier Universitaire St. Pierre; D. De Bels, Brugmann University Hospital; S. Anane, Europe Hospitals St. Elisabeth, and S. Brimioulle, M. Van Nuffelen, Erasme University Hospital — all in Brussels; M. VanCutsem, Centre Hospitalier Universitaire de Charleroi, Charleroi, Belgium; J. Rico, J.I. Gomez Herreras, Rio Hortega University Hospital, Valladolid, Spain; H. Njimi (trial statistician), Université Libre de Bruxelles, Brussels; and C. Mélot (independent statistician and physician responsible for conducting sequential analysis and evaluation of serious adverse effects), Erasme University Hospital, Brussels.

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