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*Pediatrics* 2006;117;e1213-e1222; originally published online May 22, 2006;  
DOI: 10.1542/peds.2005-2108

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# Dopamine Versus Epinephrine for Cardiovascular Support in Low Birth Weight Infants: Analysis of Systemic Effects and Neonatal Clinical Outcomes

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The authors have indicated they have no financial relationships relevant to this article to disclose.

## ABSTRACT

**BACKGROUND.** Early postnatal adaptation to transitional circulation in low birth weight infants frequently is associated with low blood pressure and decreased blood flow to organs. Catecholamines have been used widely as treatment, despite remarkably little empirical evidence on the effects of vasopressor/inotropic support on circulation and on clinically important outcomes in sick newborn infants.

**AIMS.** To explore the effectiveness of low/moderate-dose dopamine and epinephrine in the treatment of early systemic hypotension in low birth weight infants, evaluate the frequency of adverse drug effects, and examine neonatal clinical outcomes of patients in relation to treatment.

**DESIGN/METHODS.** Newborns of <1501-g birth weight or <32 weeks of gestational age, with a mean blood pressure lower than gestational age in the first 24 hours of life, were assigned randomly to receive dopamine (2.5, 5, 7.5, and 10  $\mu\text{g}/\text{kg}$  per minute;  $n = 28$ ) or epinephrine (0.125, 0.250, 0.375, and 0.5  $\mu\text{g}/\text{kg}$  per minute;  $n = 32$ ) at doses that were increased stepwise every 20 minutes until optimal mean blood pressure was attained and maintained (responders). If this treatment was unsuccessful (nonresponders), sequential rescue therapy was started, consisting first of the addition of the second study drug and then hydrocortisone.

**OUTCOME MEASURES.** These included: (1) short-term changes (first 96 hours, only responders) in heart rate, mean blood pressure, acid-base status, lactate, glycemia, urine output, and fluid-carbohydrate debit; and (2) medium-term morbidity, enteral nutrition tolerance, gastrointestinal complications, severity of lung disease, patent ductus arteriosus, cerebral ultrasound diagnoses, retinopathy of prematurity, and mortality.

**RESULTS.** Patients enrolled in this trial did not differ in birth weight or gestational age (1008  $\pm$  286 g and 28.3  $\pm$  2.3 weeks in the dopamine group; 944  $\pm$  281 g and 27.7  $\pm$  2.4 weeks in the epinephrine group). Other main antenatal variables were also comparable. However, responders and nonresponders differed significantly with

[www.pediatrics.org/cgi/doi/10.1542/peds.2005-2108](http://www.pediatrics.org/cgi/doi/10.1542/peds.2005-2108)

doi:10.1542/peds.2005-2108

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### Key Words

dopamine, epinephrine, adverse effects, preterm infants, outcome assessment

### Abbreviations

CRIB—Critical Risk Index for Babies

LBW—low birth weight

MBP—mean blood pressure

BPD—bronchopulmonary dysplasia

PDA—patent ductus arteriosus

PROM—premature rupture of membranes

HFO—high-frequency oscillatory ventilation

Accepted for publication Dec 14, 2005

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275). Copyright © 2006 by the American Academy of Pediatrics

respect to the need for cardiorespiratory resuscitation at birth (3% vs 23%), Critical Risk Index for Babies score ( $3.8 \pm 3$  vs  $7 \pm 5$ ), and premature rupture of membranes >24 hours (39.5% vs 13.6%), respectively. No differences were found in the rate of treatment failure (dopamine: 36%; epinephrine: 37%) or need for rescue therapy according to treatment allocation. Groups did not differ in age at initiation of therapy (dopamine:  $5.3 \pm 3.9$  hours; epinephrine:  $5.2 \pm 3.3$  hours), but withdrawal was significantly later in the dopamine group. For short-term changes, mean blood pressure showed a significant increase from baseline throughout the first 96 hours with no differences between groups. However, epinephrine produced a greater increase in heart rate than dopamine. After treatment began, epinephrine patients showed higher plasma lactate (first 36 hours) and lower bicarbonate and base excess (first 6 hours) and received more bicarbonate. Patients in the epinephrine group also had higher glycemia (first 24 hours) and needed insulin therapy more often. Groups did not differ in urine output or fluid-carbohydrate supply during the first 96 hours. For medium-term morbidity, there were no differences in neonatal clinical outcomes in responders. However, significant differences were found in the incidence of patent ductus arteriosus, bronchopulmonary dysplasia, need for high-frequency ventilation, occurrence of necrotizing enterocolitis, and death between responders and nonresponders.

**CONCLUSIONS.** Low/moderate-dose epinephrine is as effective as low/moderate-dose dopamine for the treatment of hypotension in low birth weight infants, although it is associated with more transitory adverse effects.

**P**OSTNATAL ADAPTATION TO the circulatory changes that take place soon after birth, particularly in preterm infants, frequently results in cardiovascular compromise leading to poor systemic blood flow<sup>1,2</sup> and low blood pressure.<sup>2-4</sup> Impaired peripheral vasoregulation and dysfunction of the immature myocardium are major determinants of hemodynamic instability.<sup>5-8</sup> Different lines of research support the hypothesis that absolute hypovolemia is not as important a primary etiologic factor as the positive effect of volume expansion on either blood pressure<sup>9-11</sup> or cardiac performance, and the effect of hypovolemia on systemic blood flow<sup>10,11</sup> is transitory or absent. Therefore, inotropes, particularly catecholamines, have been widely used in newborns to treat early cardiovascular disturbances, especially low systemic blood pressure.

Vasopressors and/or inotropes that are potentially useful in preterm infants include dopamine, dobutamine, epinephrine, and norepinephrine. These drugs produce different pharmacologic effects via  $\alpha$ - and  $\beta$ -receptor stimulation.<sup>7</sup> The original dose-range recommendations were based on pharmacodynamic studies in

healthy adults. Dopamine and dobutamine are the catecholamines most frequently used to treat hemodynamic instability in low birth weight (LBW) infants. Systematic research on the effectiveness of such drugs points toward the superiority of dopamine at improving blood pressure in these patients.<sup>11-17</sup> Nevertheless, some studies in preterm infants using dopamine at doses  $>5$   $\mu\text{g}/\text{kg}$  per min suggest that dopamine exerts its effects by increasing systemic vascular resistance, which could be counterproductive for the myocardium.<sup>12,18</sup> In fact, dobutamine<sup>11,12,17</sup> and alternative strategies, such as low/moderate-dose epinephrine,<sup>19</sup> have had a better effect on cardiac performance, probably because of a predominant  $\beta$ -effect.

Aside from information about the short-term effects of these drugs on the cardiovascular system in LBW infants, little data are available on the systematic evaluation of the effects of catecholamines on neonatal morbidity and mortality,<sup>17,20</sup> so it is difficult to document specific recommendations for treatment strategies.

We conducted a randomized clinical trial to investigate the effectiveness of low/moderate-dose dopamine and epinephrine for cardiovascular support in a population of preterm infants who experienced low blood pressure at any time during the first day of life. The first part of this study, that is, the immediate changes in systemic and cerebral circulation elicited by drug infusion, was published recently.<sup>21</sup> We would like to emphasize that we used a careful approach consisting of stepwise titration to find the dose that had an optimal hemodynamic effect in individual patients, which has not been the case in previous studies, where either fixed doses or higher initial doses of these medications were used.<sup>11,12,18,19</sup> The object of the present report is the frequency of treatment-related adverse effects and the neonatal clinical outcomes of patients.

## METHODS

### Study Design

The study was conducted at the NICU of La Paz University Hospital with the approval of the hospital's Human Studies Committee and the Spanish Drug Agency of the National Ministry of Health. Between June 2002 and November 2003, all infants consecutively admitted with <24 hours of age and a birth weight of <1501 g or a gestational age <32 weeks were eligible for the study. Informed consent was obtained on admission. Infants were enrolled in the trial if they developed arterial systemic hypotension, defined as mean blood pressure (MBP) lower than the infant's gestational age that persisted  $\geq 60$  minutes at any time in the first day of life. Exclusion criteria were life-threatening congenital defects, congenital hydrops, frank hypovolemia (perinatal history consistent with decreased circulating blood volume and clinical signs of hypovolemia), or other unre-

solved causes of hypotension (air leaks, lung overdistension, or metabolic abnormalities).

Patients were monitored continuously for heart rate, peripheral oxygen saturation (Fastrac, Critikon, Tampa, FL), and transcutaneous  $P_{CO_2}$  (Microgas 7650, Kontron Instruments, Zurich, Switzerland). In addition, several patients also underwent continuous transcutaneous  $P_{O_2}$  monitoring (Microgas 7650, Kontron Instruments). Invasive arterial monitoring with umbilical artery catheters or oscillometry (V24C, Hewlett Packard, Palo Alto, CA) was used to measure blood pressure changes. Blood arterial and/or venous samples were obtained through umbilical lines. Central venous catheters were positioned at midatrial level or at the transition between the inferior vena cava and right atrium. Clinical outcome variables were recorded prospectively for further analysis. These data were abstracted from the charts with permission, according to hospital protocols.

## Study Protocol

### Intervention

After consent and enrollment, hypotensive patients were assigned randomly to receive either dopamine or epinephrine. The study drug was increased stepwise every 20 minutes until MBP considered optimal was attained and maintained (treatment success or response). Dose increments were 2.5, 5, 7.5, and 10  $\mu\text{g}/\text{kg}$  per minute for dopamine and 0.125, 0.250, 0.375, and 0.5  $\mu\text{g}/\text{kg}$  per minute for epinephrine.

MBP considered optimal in this trial was defined as a 15% increase over the lower limit of MBP established in each infant by gestational age. The study drug was delivered by continuous infusion through a peripheral cannula or central venous line (the latter inserted peripherally or via the umbilical vein catheter) using calibrated infusion pumps. Details on masking procedures are given elsewhere.<sup>21</sup>

The first part of this trial, that is, double-blind, cerebral hemodynamics monitoring while attempting to normalize blood pressure, was considered complete after achieving 1 hour of stable optimal MBP in responders. If the vasopressor/inotrope failed to normalize blood pressure according to protocol (treatment failure or nonresponse), the study concluded 20 minutes after the last dose increase. At the end of the study, the study drugs were reconstituted at a higher concentration, and additional upward or downward changes in the infusion rate were made in accordance with the study protocol. If a maximum rate was reached and hypotension persisted (failure criteria) or responders subsequently failed to maintain the desired MBP in the following hours, the other study drug was added after the same escalation protocol. Infants with vasopressor-resistant hypotension, defined as persistently low MBP when maximum dopamine (10  $\mu\text{g}/\text{kg}$  per minute) plus epinephrine (0.5

$\mu\text{g}/\text{kg}$  per minute) doses were reached, received hydrocortisone (1 mg/kg per dose).<sup>22</sup> The results reported in this study are from the second part of this trial, an open study.

### Short-term Outcome Measures

Short-term outcomes were defined as changes that occurred in the variables considered for analysis during the first 96 hours of postnatal life. Changes in MBP and heart rate were evaluated from baseline (before giving the vasopressor/inotrope) and every 6 hours after initiation of the study drug. Blood arterial or venous samples were obtained at baseline, every 6 hours during the first day, and then every 12 hours up to 96 hours for analysis of blood gases, acid-base status, and lactate and glucose concentrations.

Finally, urine output (oliguria was defined as urine output  $<0.5$  mL/kg per hour for  $>24$  hours), fluid (mL/kg per day), and carbohydrate (g/kg per day) debit and the need for insulin therapy were also analyzed. Serum creatinine was measured at baseline and on day 3 of life, at least, and was considered abnormal if levels were  $>1.5$  mg/dL.

### Medium-term Outcome Measures

The severity of the initial lung disease and subsequent evolution were evaluated in terms of the need for mechanical ventilation or surfactant treatment, duration of respiratory support, and rate of development of bronchopulmonary dysplasia (BPD), which was defined as oxygen dependency at 36 weeks' postconceptional age. The rate of clinically significant patent ductus arteriosus (PDA) and the need for treatment also were evaluated. Tolerance of enteral nutrition included analysis of the postnatal age at which full enteral nutrition was reached, as well as the rate of complications, such as necrotizing enterocolitis and/or bowel perforation.

After randomization and before drug administration, a complete cerebral ultrasound scan was made to detect white matter damage or germinal matrix-intraventricular hemorrhage, defined according to a standardized cerebral ultrasound reporting system published elsewhere.<sup>23,24</sup> Posthemorrhagic hydrocephalus was diagnosed in the presence of progressive ventricular dilatation.<sup>25</sup> Persistent periventricular echogenicity was considered to be present if abnormal parenchymal hyperechogenicity lasted  $>14$  days.<sup>23</sup> All of the early deaths and patients who developed posthemorrhagic hydrocephalus before 14 days were excluded from this particular analysis. Serial ultrasound scans were repeated weekly in every patient up to 40 weeks' postconceptional age or death. The final cerebral ultrasound study for each patient was defined as the ultrasound study showing the most severe damage for each diagnosis before death or at 40 weeks' postconceptional age. The initial and final cerebral ultrasound diagnoses are given

in this study. All of the cerebral ultrasound studies were made by the same investigator (F.C.), who did not know what drug was being given.

### Statistical Analysis

Details regarding sample size and random assignment are reported elsewhere.<sup>21</sup> Data were analyzed with SPSS for Windows software (release 9.0, SPSS Inc, Chicago, IL). Quantitative data are given as mean  $\pm$  SD and qualitative data as counts or percentages. Comparisons between groups were tested with the Mann-Whitney rank-sum test and either Fisher's exact test or the  $\chi^2$  test for quantitative and qualitative data, respectively.

The population considered for the analysis of primary outcomes (short- and medium-term outcome measures) included patients who received only the initial vasopressor/inotrope (responders). These patients were also compared with those who needed rescue therapy (nonresponders) with respect to different perinatal and postnatal outcomes.

To determine which factors were independently associated with treatment failure, multivariate stepwise logistic regression analysis was performed. All of the statistical analyses were considered bilateral. Values of  $P < .05$  were considered significant.

## RESULTS

### Study Groups

In the 17-month study, 206 infants  $<24$  hours old with a gestational age  $<32$  weeks and/or birth weight  $<1501$  g were admitted consecutively to the NICU. Details regarding the flow of participants through each stage of the trial and reasons for exclusions can be found elsewhere.<sup>21</sup> Sixty of the 86 patients who did not meet any exclusion criteria and developed systemic hypotension on the first day of life were enrolled in the study, representing 70% of eligible infants. Mean gestational age ( $28 \pm 2.3$  vs  $28.2 \pm 2.3$  weeks) and birth weight ( $978 \pm 282$  vs  $1050 \pm 313$  g) did not differ between the infants enrolled and the infants not enrolled. Other clinical variables, such as gender, multiple births, use of antenatal steroids or surfactant, and the type of ventilatory support, were also similar.

The 60 patients randomized were assigned to receive dopamine ( $n = 28$ ) or epinephrine ( $n = 32$ ) as vasopressor/inotrope therapy. Patients in the 2 groups did not differ in birth weight or gestational age. Invasive arterial monitoring was used in 52 patients (26 in the dopamine group and 26 in the epinephrine group). Umbilical venous catheters were inserted in 22 patients (11 patients per group). Details on relevant clinical data at the time of entry into the study can be found elsewhere.<sup>21</sup>

Catecholamine infusion started at a mean age of  $5.3 \pm 3.7$  hours of life. Twenty-one patients (10 in the dopamine group and 11 in the epinephrine group) had

received volume expanders (10–15 mL/kg), at a mean time of  $3.5 \pm 2.4$  hours before randomization. None of the infants enrolled received indomethacin before the vasopressor/inotrope.

No differences were found between groups in the use of antenatal steroids, chorioamnionitis (defined by either clinical or clinical and pathologic criteria), premature rupture of membranes (PROM)  $>24$  hours, type of resuscitation at birth, Apgar score, intrauterine growth restriction, gender, or Critical Risk Index for Babies (CRIB) score. The clinical condition of the infants at the time of randomization was also comparable. Comparisons between patients with treatment success (responders) and patients with treatment failure (nonresponders) yielded statistically significant differences in the need for cardiorespiratory resuscitation at birth (3% vs 23%;  $P < .05$ ), CRIB score ( $3.8 \pm 3$  vs  $6.8 \pm 4.9$ ;  $P < .05$ ), and PROM  $>24$  hours (39.5% vs 13.6%  $P < .05$ ). The last association disappeared when an analysis stratified by the use of antenatal steroids was made. No differences were found in other conditions at birth, such as arterial/venous umbilical cord pH ( $7.23 \pm 0.13/7.27 \pm 0.14$ ,  $n = 27$ , in responders vs  $7.23 \pm 0.14/7.27 \pm 0.14$ ,  $n = 16$ , in nonresponders) or first hour pH ( $7.31 \pm 0.09$  vs  $7.28 \pm 0.09$ ), base excess ( $-5.2 \pm 4.1$  vs  $-6.6 \pm 4.6$ ), and bicarbonate ( $20.3 \pm 3.7$  vs  $19.9 \pm 4.1$ ). Relevant clinical data are summarized by drug assigned and treatment response in Table 1.

### Primary Outcomes (Responders)

#### Short-term Outcomes

Treatment was successful in 63% of patients, who attained and maintained normal MBP ranges according to protocol as a result of vasopressor support with the initial drug. The rate of treatment failure did not differ between groups. The use of rescue treatment, including volume expanders, other inotropes, or hydrocortisone, was also similar in both groups. However, groups differed significantly in postnatal age at the time of drug withdrawal, with dopamine-treated patients being significantly older ( $66 \pm 28$  hours in the dopamine group,  $38 \pm 20$  hours in the epinephrine group;  $P < .01$ ).

The profiles of changes in MBP and heart rate throughout the first 96 hours of life are shown in Fig 1. Groups did not differ with respect to MBP (Fig 1 A). Heart rate changes varied by group, the increase in heart rate being significantly higher in the epinephrine group than in the dopamine group 6 and 12 hours after inotrope infusion began ( $P < .05$ ; Fig 1 B).

Baseline conditions were similar in terms of metabolic parameters, but the pattern of changes after starting drug infusion differed between groups. Epinephrine patients showed an increase in plasma lactate levels, which remained significantly higher than in the dopamine group during the first 36 hours (Fig 2 A). These patients

**TABLE 1 Perinatal Data of Study Population According to Treatment Response**

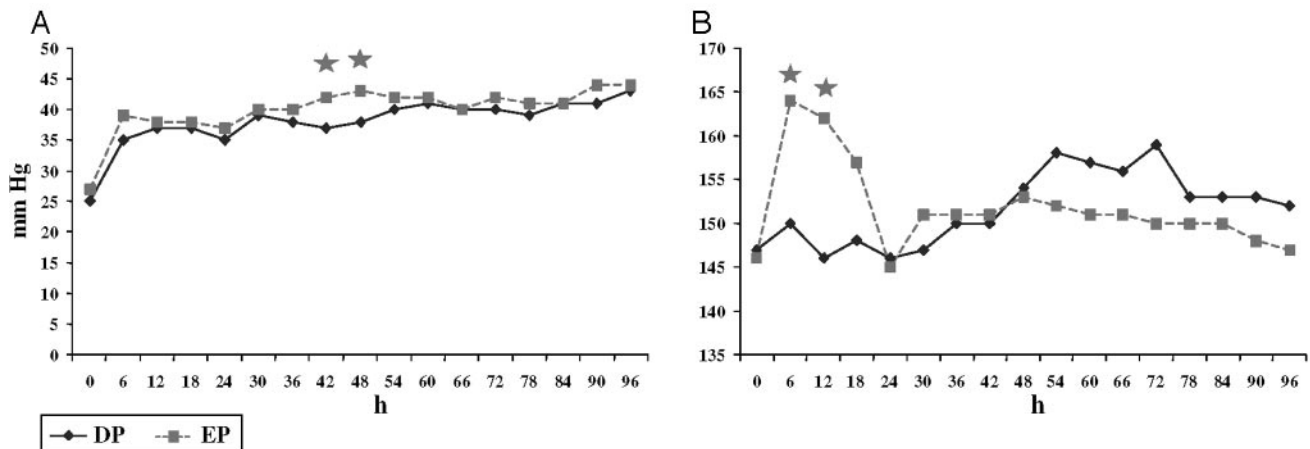
Variable	Responders (treatment success)			Nonresponders (treatment failure; <i>n</i> = 22)
	DP ( <i>n</i> = 18)	EP ( <i>n</i> = 20)	Total ( <i>n</i> = 38)	
Male, <i>n</i> (%)	6 (33)	9 (45)	15 (39)	12 (54)
Multiple births, <i>n</i> (%)	7 (39)	7 (35)	14 (37)	8 (38)
Vaginal delivery, <i>n</i> (%)	8 (44)	6 (30)	14 (37)	6 (27)
Gestational age, wk, mean ± SD	28.5 ± 2.1	28.3 ± 2.2	28.4 ± 2.1	27.5 ± 2.5
Birth weight, g, mean ± SD	1069 ± 257	980 ± 281	1022 ± 270	892 ± 271
Apgar score (5')	7 ± 1.6	7 ± 1.2	7 ± 1.4	6.5 ± 1.6
Umbilical cord pH (arterial) <sup>a</sup>	7.25 ± 0.13	7.21 ± 0.12	7.23 ± 0.13	7.23 ± 0.14
First hour pH	7.31 ± 0.10	7.32 ± 0.08	7.31 ± 0.09	7.28 ± 0.09
CRIB score <sup>b</sup>	4 ± 2.9	3.7 ± 3.1	3.8 ± 3	6.8 ± 4.9
Antenatal steroids, <i>n</i> (%) <sup>c</sup>	13 (72.2)	14 (70)	27 (71.1)	12 (54.5)
Chorioamnionitis, <i>n</i> (%)	5 (28)	5 (25)	10 (26)	3 (14)
PROM >24 hours, <i>n</i> (%) <sup>b</sup>	6 (33.3)	9 (45)	15 (39.5)	3 (13.6)
IQR, <i>n</i> (%)	2 (11)	6 (30)	8 (21)	3 (14)

IQR indicates intrauterine growth restriction; PROM >24 hours, premature rupture of membranes >24 hours before birth.

<sup>a</sup> Umbilical cord arterial blood sampling (dopamine = 12; epinephrine = 15; failure = 16).

<sup>b</sup> Success versus failure (Fisher's exact test, *P* < .05).

<sup>c</sup> Antenatal steroids indicates a complete course.



**FIGURE 1**

Changes in MBP (A) and heart rate (B) throughout the first 96 hours of life, evaluated from baseline, before giving the inotrope (time 0) and then every 6 hours. Only responders. Star indicates *P* < .05.

also showed a similar profile of blood glucose levels: blood glucose increased significantly with respect to baseline values and remained significantly higher during the first 24 hours (Fig 2 B). Base excess (Fig 2 C) and serum bicarbonate levels (Fig 2 D) were significantly lower in the epinephrine group at 6 hours of treatment and increased progressively thereafter. No differences were found between groups in pH at baseline or during evolution. However, infants in the epinephrine group received bicarbonate more frequently during the first 96 hours (dopamine: 67%, epinephrine: 95%; *P* < .05).

Groups did not differ with respect to urine output or 24-hour fluid supply (Table 2). Baseline and day-3 creatinine serum levels were also comparable. No differences between groups were found in the rate of creatinine serum levels >1.5 mL/dL. Potassium serum levels

at baseline and during the first 96 hours of life were similar in both groups.

During the first 4 days of life, patients in both groups received similar amounts of intravenous carbohydrates (Table 2). However, insulin therapy was used significantly more often during the first 96 hours in epinephrine-treated infants (12% in the dopamine group and 45% in the epinephrine group; *P* < .05).

#### Medium-term Outcomes

The main clinical outcomes according to drug allocation are shown in Table 3. The frequency of lung disease between groups was comparable, because no differences were found in the incidence of respiratory distress syndrome; surfactant therapy; BPD; and need for, type of, or time on mechanical ventilation (Table 3). Although

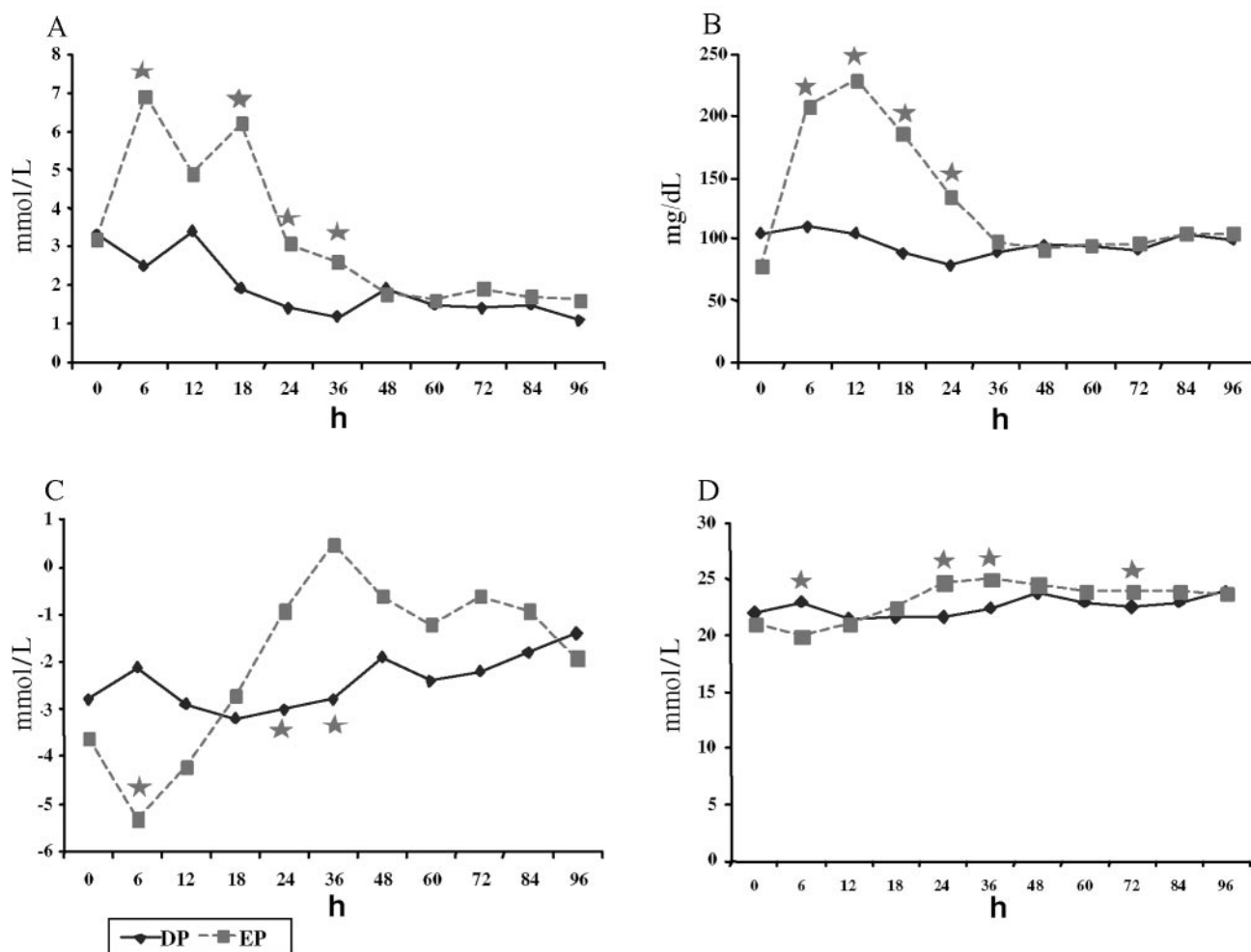


FIGURE 2

Evolution of metabolic parameters in responders: changes in serum lactate (A), glucose (B), base excess (C), and bicarbonate (D) from baseline before giving the inotrope (time 0) and throughout the first 96 hours of life are displayed. Star indicates  $P < .05$ .

TABLE 2 First 96 Hours of Renal Function and Fluid/Carbohydrate Debits in Responders

Day	Inotrope	Fluid Intake mL/kg per Day	Carbohydrate g/kg per Day	Urine Output mL/kg per Hour	Serum Creatinine mg/dL
First day <sup>a</sup>	Dopamine	81 ± 14	5.1 ± 1.4	2.6 ± 1.1	0.85
	Epinephrine	85 ± 26	5.6 ± 1	3.3 ± 1.5	0.87
Second day <sup>a</sup>	Dopamine	74 ± 9	6.6 ± 1.4	4.2 ± 1.2	
	Epinephrine	87 ± 24	6.7 ± 1.3	4.0 ± 1.4	
Third day <sup>a</sup>	Dopamine	90 ± 15	8.3 ± 1.1	3.8 ± 1.2	0.93
	Epinephrine	100 ± 19	8.4 ± 1.6	3.6 ± 1.2	0.88
Fourth day <sup>a</sup>	Dopamine	104 ± 26	9.8 ± 1.3	3.7 ± 1.4	
	Epinephrine	116 ± 19	10 ± 1.5	3.7 ± 1.3	

<sup>a</sup> Mann-Whitney test, dopamine versus epinephrine (not significant).

more patients in the dopamine group had PDA, differences were not statistically significant. The rates of pharmacologic or surgical closure were also similar between groups. Finally, no differences between groups were found in the tolerance of enteral nutrition, gastrointestinal complications, sepsis, severe retinopathy, or mortality.

Initial cerebral ultrasound diagnoses were (Table 4) moderate-to-severe periventricular hyperechogenicity

in 18 patients and grade 1–2 germinal matrix-intraventricular hemorrhage in 12 patients. Some patients had both sonographic findings. The initial cerebral ultrasound evaluation was normal in 33 infants. No differences were found between groups in the final cerebral ultrasound diagnosis obtained in follow-up evaluations (Table 4). Some infants had >1 cerebral ultrasound finding. Twenty-seven infants exhibited normal sonograms at follow-up.

**TABLE 3 Clinical Outcomes of Study Population**

Variable	Success			Failure (n = 22)
	Dopamine (n = 18)	Epinephrine (n = 20)	Total (n = 38)	
PDA, n (%) <sup>a</sup>	6 (33.3)	3 (15)	9 (23.7) <sup>b</sup>	11 (52.4) <sup>b</sup>
Respiratory support, n (%) <sup>c</sup>	18 (100)	20 (100)	38 (100)	22 (100)
HFO, n (%)	5 (28)	4 (20)	9 (24) <sup>b</sup>	14 (64) <sup>b</sup>
Days on respiratory support, mean (SD)	7 (11)	6 (10)	6.5 (11)	13 (15)
Sedation, n (%) <sup>d</sup>	8 (44)	4 (20)	12 (32)	9 (41)
Surfactant treatment, n (%)	12 (67)	13 (65)	25 (66)	18 (86)
BPD, n (%) <sup>e</sup>	2 (11)	1 (5)	3 (8) <sup>b</sup>	8 (57) <sup>b</sup>
Early sepsis, n (%)	2 (11.1)	3 (15)	5 (13.2)	2 (9.5)
Delayed sepsis, n (%) <sup>f</sup>	8 (44.4)	6 (30)	14 (36.8)	6 (33.3)
Full enteral nutrition, day, mean (SD) <sup>g</sup>	18 (9)	20 (15)	19 (12)	22 (13)
Necrotizing enterocolitis, n (%) <sup>g</sup>	1 (5.6)	-	1 (2.7) <sup>b</sup>	4 (25) <sup>b</sup>
Bowel perforation, n (%) <sup>g</sup>	1 (5.6)	-	1 (2.7)	1 (6.3)
ROP-laser, n (%) <sup>h</sup>	1 (5.9)	1 (5.9)	2 (5.9)	1 (7.1)
Deceased, n (%)	1 (5.6)	1 (5)	2 (5.3) <sup>b</sup>	7 (31.8) <sup>b</sup>

<sup>a</sup> PDA, excluding 1 patient deceased at 9 hours (dopamine = 18, epinephrine = 20, failure = 21).

<sup>b</sup> Success versus failure (Fisher's exact test),  $P < .05$ .

<sup>c</sup> Respiratory support means continuous nasal end-expiratory pressure, synchronized intermittent mandatory ventilation, or HFO.

<sup>d</sup> Sedation means midazolam, fentanyl, or both.

<sup>e</sup> BPD considered only in infants surviving up to 36 weeks postconception (dopamine = 18, epinephrine = 19, failure = 14).

<sup>f</sup> Only considered if survival >72 hours (dopamine = 18, epinephrine = 20, failure = 18).

<sup>g</sup> Only considered if survival >14 days and infant received enteral nutrition (dopamine = 18, epinephrine = 19, failure = 16).

<sup>h</sup> ROP-laser means retinopathy requiring laser therapy considered only in infants who survived  $\geq 5$ -6 weeks and had studies (dopamine = 17, epinephrine = 17, failure = 14).

**TABLE 4 Cerebral Ultrasound Diagnoses**

CUS Diagnosis	Initial (before inotrope)			Failure <sup>c</sup> (n = 22)	Final			Failure <sup>c</sup> (n = 22)
	Success <sup>c</sup>				Success <sup>c</sup>			
	Dopamine <sup>b</sup> (n = 18)	Epinephrine <sup>b</sup> (n = 20)	Total (n = 38)		Dopamine <sup>b</sup> (n = 18)	Epinephrine <sup>b</sup> (n = 20)	Total (n = 38)	
Normal	8	13	21	12	7	11	18	9
Grade 1-2 IVH	5	4	9	3	6	6	12	6
Grade 3 IVH	-	-	-	-	3	-	3	5
PVHI	-	-	-	-	1	-	1	3
Moderate-severe PVE	6	4	10	8				
Persistent PVE <sup>a</sup>					5	3	8	5
Cystic PVL <sup>a</sup>					-	2	2	-
Posthemorrhagic hydrocephalus					3	-	3	2

CUS indicates cerebral ultrasound; IVH, intraventricular hemorrhage; PVHI, periventricular hemorrhagic infarction; PVL, periventricular leukomalacia; PVE, periventricular echogenicity

<sup>a</sup> Considered only if survival >14 days without posthemorrhagic hydrocephalus (dopamine = 18, epinephrine = 19, failure = 16).

<sup>b</sup> Fisher's exact test (not significant): dopamine versus EP (success).

<sup>c</sup> Fisher's exact test (not significant): success versus failure.

### Outcome According to Treatment Response

Considering the overall study population, comparisons between responders and nonresponders disclosed differences in several clinical outcomes. Patients who failed to normalize blood pressure differed significantly from responders in incidence of PDA, necrotizing enterocolitis, BPD, and need for high-frequency oscillatory ventilation (HFO) ( $P < .05$ ; Table 3).

Stepwise multiple logistic regression analysis with type of resuscitation, birth weight, CRIB score, HFO, and PDA as independent variables and treatment failure as the dependent variable disclosed HFO (odds ratio: 4.2; 95% confidence interval: 1.25-14.09) and PDA (odds

ratio: 3.32; 95% confidence interval: 0.98-11.29) as factors that independently influenced treatment failure.

Nonresponders also received significantly larger amounts of fluid during the first day of life ( $98 \pm 24$  mL/kg per day in the treatment failure group vs  $83 \pm 23$  mL/kg per day in the treatment success group;  $P < .01$ ) and second day of life ( $121 \pm 53$  mL/kg per day in the treatment failure group vs  $81 \pm 19$  mL/kg per day in the treatment success group;  $P < .001$ ). No differences in either the initial or final cerebral ultrasound diagnoses were found between responders and nonresponders (Table 4).

Overall mortality was 15%, with no differences by drug assigned. Seven of the 9 deceased patients were

infants with treatment failure who received rescue therapy ( $P < .001$ ). All of the deaths occurred during the neonatal period (days 1–21 of life) except for 1 infant (3 months of age).

## DISCUSSION

This is the first randomized clinical trial of cardiovascular support with inotropes to evaluate prospectively and systematically the frequency of adverse effects and the short- and medium-term clinical outcomes of LBW infants treated for systemic hypotension soon after birth. The first part of this trial, that is, the blinded evaluation of the effects of vasopressors/inotropes on brain hemodynamics, was the subject of a recent report.<sup>21</sup> This is also the first prospective study to report the effects of continuous infusion of epinephrine in LBW infants. This is important because epinephrine usually is considered second-line treatment for normovolemic shock resistant to other vasopressors.

According to the dosing regimens used in this study, cardiovascular support with either dopamine or epinephrine was successful in 63% of patients who received treatment with the initial vasopressor/inotrope alone; the effectiveness of these 2 catecholamines in increasing and maintaining an adequate MBP according to protocol was similar in this study. Although this study was not designed to determine the causes of hemodynamic instability and/or their influence on response to treatment, it is remarkable that the incidence of PDA and the need for HFO were significantly more frequent in nonresponders who received rescue therapy. In fact, these conditions were factors that independently influenced treatment response.

MBP showed a significant increase from baseline that was independent of drug group. This change in MBP was maintained regardless of scaling-down or discontinuing the dose of vasopressor/inotrope infusion during the first 96 hours of life. This is probably because the statistically defined lower limits of MBP are dependent on postnatal age, so even in the most immature patients, MBP is  $\geq 30$  mm Hg by day 3 of life.<sup>26</sup>

Epinephrine infusion was associated with a greater chronotropic effect, because a significantly greater increase in heart rate was observed in the epinephrine group than in dopamine-treated infants in the first 12 hours of this study. This effect is observed quickly, even at very low doses, as has been reported recently by our group.<sup>21</sup> Epinephrine infusions and their cardiovascular effects have been investigated in a limited way in neonatal animal models.<sup>27–30</sup> Reports on adult humans using the same dosing regimens as used in the present study found that epinephrine and dopamine infusions at peak dose were associated with significant mean increases in cardiac index, although these increases were higher with epinephrine than with dopamine.<sup>31</sup> Data from human newborns, particularly preterm infants, is scarce. A single study<sup>32</sup> describes the effects of a continuous infusion of epinephrine in LBW infants, although this was not a

randomized trial, and, in most cases, patients received concomitant treatment with dopamine.

A limitation of the study is that, aside from heart rate and blood pressure, circulatory effects were not measured. Consequently, the interpretation of results is, to some extent, speculative and based on indirect observations. However, if these drugs behave the same in systemic circulation as they do in cerebral circulation, we can infer from our observations of the effects on cerebral perfusion and oxygenation<sup>21</sup> that the increase in MBP as a result of cardiovascular support after the protocol used in this study results in a real increase in systemic blood flow. Previous studies have reported a decrease in cardiac performance with dopamine infusion<sup>11,12,19</sup> but not with epinephrine infusion.<sup>19</sup> However, these protocols used higher doses of dopamine, which could account for an increase in systemic vascular resistance resulting in myocardial depression. Different studies favor the use of dopamine dose ranges of 2–10  $\mu\text{g}/\text{kg}$  per minute to treat preterm infants with impaired cardiovascular function<sup>33–35</sup> based on developmental changes in the sensitivity of adrenergic receptors to dopamine and on the maturation of hepatic and renal clearance mechanisms.<sup>35</sup> This study also indicates that low doses of vasopressors/inotropes are effective for the treatment of early hypotension in LBW infants, and stepped doses should be used until the desired MBP is achieved in individual patients.

With respect to renal function, urine flow and creatinine serum levels did not differ between groups. Infants received similar amounts of intravenous fluids during the first 4 days of life. Although neonatal animal models do not support any renal vasodilator effect of dopamine at any dose,<sup>36</sup> studies in preterm infants receiving low-dose dopamine have shown a diuretic and saluretic effect<sup>35</sup> or only a natriuretic effect but nonsignificant increases in glomerular filtration rate and urine volume.<sup>34</sup> In addition, low/moderate-dose dopamine elicited a diuretic and renal vasodilatory response in preterm infants.<sup>37</sup> In either normovolemic or hypovolemic awake newborn piglets, epinephrine doses  $< 1.6 \mu\text{g}/\text{kg}$  per minute do not produce vasoconstriction of the renal circulation.<sup>29</sup> It is remarkable that, although postnatal age at drug withdrawal was significantly greater in the dopamine group in this study, this apparently had no beneficial effect on urine flow.

After the onset of vasopressor/inotrope infusion, epinephrine-treated patients showed higher plasma lactate levels, lower base excess and bicarbonate, and received bicarbonate more frequently compared with dopamine-treated patients. This increase in plasma lactate was coupled with significantly higher blood glucose levels despite comparable rates of carbohydrate supply in the 2 groups; the epinephrine group also needed insulin more frequently.

Dopamine and epinephrine delivered in the same dose ranges used in our protocol produce similar effects

on base excess and lactate in critically ill human adults.<sup>31</sup> Perfusion of either drug increases oxygen delivery and consumption and decreases oxygen extraction.<sup>31</sup> In our previous report,<sup>21</sup> we found similar or even higher end-of-study central venous oxygen saturation than at baseline, which could be interpreted in 2 ways: increased left-to-right atrial shunting through the foramen ovale or adequate systemic blood flow and oxygen supply as a result of vasopressor treatment. Although blood lactate concentration is used as a marker of anaerobic respiration resulting from cellular hypoxia, a poor correlation between common acid-base parameters and blood lactate concentrations has been found in critically ill neonates.<sup>38</sup> On the other hand, epinephrine infusion produces major effects on carbohydrate metabolism and a rise in plasma lactate mediated by  $\beta_2$ -adrenoceptor stimulation,<sup>39,40</sup> causing increased skeletal muscle glycogenolysis together with hepatic glycogenolysis and gluconeogenesis. Therefore, the increase in blood glucose concentration, greater demand for insulin therapy despite similar carbohydrate delivery, and increase in blood lactate levels in epinephrine-treated infants found in this study could be also attributed to  $\beta_2$ -adrenoceptor stimulation. The fact that baseline and evolutive potassium serum levels were comparable between groups favors this hypothesis as opposed to inadequate tissue blood flow and oxygen supply.

Because one of the outcome measures of this study was to evaluate potential differences in main clinical outcomes according to treatment assigned, only patients who received a single vasopressor/inotrope, that is, the initial medication, were considered for this analysis (Table 3). Patients did not differ with respect to important clinical outcomes, such as respiratory disease and progression to BPD, incidence of PDA, treatment response, and rate of early or delayed sepsis. Days to reach full enteral nutrition and the incidence of gastrointestinal complications, like bowel perforation and/or necrotizing enterocolitis, were also similar. Finally, groups did not differ in either the incidence of severe retinopathy needing laser therapy or mortality.

The evolution of the study population according to treatment response differed significantly in several clinical outcomes. Patients who failed to maintain MBP and needed rescue treatment (nonresponders) required larger intravenous flow rates during the first 2 days of life and showed higher rates of BPD than responders. These 2 patient populations also differed in the incidence of necrotizing enterocolitis and mortality, both of which were significantly higher in nonresponders, suggesting that sustained poor systemic perfusion that indirectly reinforced early cardiovascular stabilization was determinant of unfavorable outcome. Although prolonged vasopressor-resistant hypotension and aggressive management of the condition could have had an impact on organ blood flow, this could not be ascertained in this study. Moreover, other perinatal factors could have in-

fluenced patient outcome. For instance, nonresponders were in poorer condition at birth, more frequently requiring cardiopulmonary resuscitation and showing higher CRIB scores than responders. Nonresponders had lower birth weight, and antenatal steroids were used less frequently, although these findings were not significant. PROM >24 hours was significantly more frequent in responders, although this could be explained by the higher rates of administration of a complete course of antenatal steroids in this group. In fact, when we made a stratified analysis by use of antenatal steroids, the association between PROM >24 hours and success disappeared.

This study population did not differ with respect to cerebral ultrasound diagnoses before and after vasopressor treatment (Table 4). Despite pressure-passive cerebral circulation,<sup>21</sup> no differences were found in the severity of cerebral ultrasound diagnoses between responders and nonresponders. Nevertheless, mortality rates were higher in nonresponders, which could explain in part the absence of differences in certain sonographic findings. Although there is concern about the use of catecholamines and their potential to increase the risk of intraventricular hemorrhage,<sup>41</sup> our study cannot be used to claim that early stabilization of blood pressure by vasopressor/inotrope treatment is either safe or convenient in terms of preventing neurologic injury.

## CONCLUSIONS

We conclude that low-dose epinephrine is as effective as low/moderate-dose dopamine in increasing systemic MBP in LBW infants and has a more intense chronotropic effect. Because the results of this study disclosed no differences in major neonatal clinical outcomes between treatment groups, no firm recommendations can be made on the choice of drug to treat hypotension. However, the transitory adverse effects of epinephrine on carbohydrate and lactate metabolism could undermine the use of epinephrine as a first-line inotrope in preterm infants who are prone to such metabolic disturbances. Although this effect seems to be because of  $\beta_2$ -adrenergic stimulation, more studies are needed to understand the effects of these inotropes on tissue perfusion and oxygen supply in this population of LBW infants. Finally, PDA, need for HFO ventilation, and severity of disease shortly after birth are associated with failure to stabilize blood pressure with inotrope treatment. The need for >1 inotrope to treat early cardiovascular compromise is accompanied by a higher morbidity and mortality in LBW infants.

## ACKNOWLEDGMENT

This work was supported by Instituto de Salud Carlos III grant FIS 02/1110.

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# Dopamine Versus Epinephrine for Cardiovascular Support in Low Birth Weight Infants: Analysis of Systemic Effects and Neonatal Clinical Outcomes

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*Pediatrics* 2006;117:e1213-e1222; originally published online May 22, 2006;  
DOI: 10.1542/peds.2005-2108

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