Randomized, Placebo-Controlled Trial of Dobutamine for Low Superior Vena Cava Flow in Infants

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Objective To gather information for a future confirmatory trial of dobutamine (DB) for circulatory impairment (ie, low superior vena cava [SVC] flow).

Study design A total of 127 infants born at <31 weeks gestational age were serially scanned from birth to 96 hours after birth. The infants were randomly assigned to 2 groups and were treated with DB (stepwise dose increase, 5-10-15-20 μg/kg/min) or placebo if they had an SVC flow <41 mL/kg/min within the first 24 hours after birth. The primary outcome measures were the achievement and maintenance of an SVC flow ≥41 mL/kg/min. Secondary outcome measures were the short-term evolution of clinical and biochemical variables, near-infrared spectroscopy, cranial Doppler ultrasound, and clinical outcomes.

Results SVC flow increased throughout the first 96 hours for the entire cohort. All of the randomized infants (n = 28) except 2 achieved and maintained an SVC flow ≥41 mL/kg/min after intervention; however, the infants treated with DB (n = 16) showed a higher heart rate and improved base excess compared with those treated with placebo (n = 12). Low SVC flow was associated with low gestational age (P = .02) and poor condition at birth (P = .02). Low SVC flow significantly increased the risk of severe ischemic events (OR, 13; 95% CI, 2.4-69.2; P < .01).

Conclusion This exploratory trial demonstrates a tendency toward improved short-term clinical and biochemical perfusion variable outcomes in infants with low SVC flow treated with DB. *(J Pediatr 2015;167:572-8).*

Trial registration ClinicalTrials.gov (NCT01605279) and the European Clinical Trials Database (EurodraCT 2009-010901-35).

The definition of poor tissue perfusion in preterm infants remains controversial.[1,2] The superior vena cava (SVC) flow represents the blood flow coming from the upper part of the body, which is unaffected by intracardiac or extracardiac shunts.[3] Low SVC flow appears to be a relevant biomarker for circulatory impairment shortly after birth. Moreover, low SVC flow is associated with intraventricular hemorrhage, adverse neurodevelopmental outcomes, and death in immature infants.[4-7]

Although a previous small randomized clinical trial found dobutamine (DB) to be superior to dopamine at increasing SVC flow,[8] the rate of treatment failure was high for both drugs. A 3-year follow-up of the surviving infants from both study arms showed no significant differences in the presence of cerebral palsy, deafness, or neurodevelopmental delay; however, the infants who received DB had a higher development quotient.[7] Despite the potential beneficial effects of DB, the efficacy and safety of DB compared with placebo for circulatory impairment have not been tested until now.

The present study is an exploratory trial aimed at gathering information on feasibility for a future confirmatory trial of DB for the treatment of preterm infants with early circulatory impairment. In this study, circulatory impairment is defined as low SVC flow (<41 mL/kg/min). For the secondary objective, the effect of DB compared with placebo was investigated for the following variables: short-term evolution of the routine clinical and biochemical measures indicating circulatory impairment; near-infrared spectroscopy (NIRS) and cranial Doppler ultrasound measurements; and the primary neonatal clinical outcomes at term equivalence.

CU	Cranial ultrasound
DB	Dobutamine
Echo-D	Echocardiography
FOE	Fractional oxygen extraction
HR	Heart rate
NIRS	Near-infrared spectroscopy
RI	Resistance index
SaO_2	Peripheral oxygen saturation
SVC	Superior vena cava
TOI	Tissue oxygenation index

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Methods

This randomized, blinded, placebo-controlled pilot trial was conducted at La Paz University Hospital in Madrid, Spain, between August 2010 and October 2012. All infants born before 28 weeks gestation and those born between 28 and 30+6 weeks who received either invasive or noninvasive ventilator support (mean airway pressure ≥4 cm H_2O or FiO_2 ≥0.3) were considered eligible for the study (**Figure 1**; available at www.jpeds.com).

The inclusion criteria for randomization to DB or placebo were SVC flow <41 ml/kg/min at any time during the first 24 hours after birth and signed informed consent. The exclusion criteria were major congenital malformations, postnatal age above 12 hours at screening and declined informed consent. The use of other type of cardiovascular support apart from DB at the time of randomization was not considered an exclusion criterion. The study protocol was approved by the Ethics Committee for Human Studies at La Paz University Hospital and the Spanish Medicines Agency at the National Ministry of Health.

Intervention Period

After consent and enrollment, the infants underwent echocardiography (Echo-D) as soon as possible in the first 12 hours of life. The infants with an SVC flow ≥41 mL/kg/min were then scanned within 60 minutes for normal SVC flow confirmation. Those with an SVC flow <41 mL/kg/min at any time during the first 24 hours after birth (low SVC flow group) were randomized into 2 groups. DB (12.5 mg/mL; Dobutamine Mayne; Mayne Pharma, Madrid, Spain) was administered to one group, and placebo was administered to the other group. Intravenous solutions were prepared in identical syringes. A nurse who was not involved in the clinical care of the infants prepared the study medication and allocated the study codes. This nurse remained the custodian of the study codes until the study was opened.

The solution concentrations were adjusted so each had a flow rate increase of 0.1 mL/h, corresponding to a stepped increase in DB dose infusion of 5-10-15-20 μg/kg/min. An equal volume of placebo (dextrose 5% in water) was administered with the same measurements.

The study protocol did not require volume expansion before the intervention. Strict standardization of the study medication administration system was maintained. The study medication was delivered through a central venous line and was connected at the stopcock closest to the catheter entry after feeding the whole system (bionector included) with the study medication solution. The effective start time of the infusion was calculated as the time at which the infusion pump was switched on plus the empirical value for the interval arising from dead space (dead space [min] = (volume [mL]/velocity [mL/h]) × 60 [min/h]), where volume refers to the catheter lumen plus the stopcock dead space and velocity refers to the summation of the infusion rates of all of the various infusions coming through the line. The infusion rate was started at 0.1 mL/h and was doubled at 30 minutes after the effective start time if no dose-limiting effects were observed. The infants were first scanned at 60 minutes after the effective start time, then 30 minutes after each rate increase until SVC flow normalization occurred (≥41 mL/kg/min), and then again at 30 minutes after normal SVC flow was achieved. Once SVC flow normalized, the study drug was maintained at the same infusion rate. The down-titration strategy was left at the discretion of the attending physician, but was always started later than 24 hours after birth. Dose reductions occurred in steps of 0.1 mL/h. If SVC flow did not normalize at the highest infusion rate (0.4 mL/h), then the treatment was considered a failure, at which point the study participant was unmasked and the attending physician provided further care. Dose-limiting effects of the study medication were tachycardia (heart rate [HR] >200 bpm after normal saline infusion) and arrhythmias. Patients were withdrawn from the study if these conditions were persistent or recurrent. Open-label treatment with other cardiovascular support guided by a constellation of routine clinical or biochemical data, mainly blood pressure, was managed according to the policy currently in place at the unit, following a standardized protocol that did not include DB.[9]

Intensive Follow-Up Period

Beyond the intervention period, serial Echo-D studies were performed at 24, 48, 72, and 96 hours after birth in the entire study population (**Figure 1**). The infants underwent continuous physiological and cerebral NIRS monitoring throughout the intervention period and at the 24-hour study time point. Cranial power Doppler studies were performed at the same time as the first Echo-D (always before randomization) and during daily assessments, up to 96 hours. To evaluate brain injury, standard cranial ultrasound (CU) imaging was performed as soon as possible on the first day, at day 7, at day 14, and at term equivalence. Additional CU studies were scheduled if clinically indicated.

The diagnoses were classified according to a previously reported system.[9,10] The operators were blinded to the infants' group allocation. Blood samples were drawn at 6-hour intervals for the analysis of biochemical variables if clinically indicated. Plasma N-terminal pro-brain natriuretic peptide and cardiac troponin I concentrations were measured at 6, 24, and 96 hours.

Trial Assessment Tools

The Vivid S5 ultrasound system (GE Healthcare, Wauwatosa, Wisconsin) was used for Echo-D and CU power Doppler studies. SVC flow was measured according to the method described by Kluckow and Evans.[3] The images were stored and reviewed offline by a single investigator, who used systematic quality assessment to approve or reject the scans.