

## Summary Proceedings From the Cardiology Group on Cardiovascular Instability in Preterm Infants

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### ABSTRACT

The appropriate determination of adequate tissue perfusion and the best approach to treatment of perceived abnormalities in blood pressure in the neonate remain controversial. There is no consensus regarding the actual definition of hypotension in the neonate or how best to raise perceived low blood pressure. In addition, there is no direct and prospectively collected information available on the result of treatment of a "low" blood pressure on neonatal morbidity and mortality. It also has not been clearly demonstrated that bringing systemic blood pressure to a "normal" range improve outcomes. However, it is widely accepted by clinicians that early and aggressive treatment of hypotension leads to improved neurologic outcome and survival in the neonate. Commonly used therapeutic maneuvers to correct systemic hypotension in the neonate include volume expansion, inotropic agents, and corticosteroids. Although there is a paucity of research on the cardiovascular response to these commonly used agents in neonates, among the commonly used inotropic drugs dopamine has been shown to be more effective than dobutamine in raising blood pressure in the neonate. The cardiology group focused on the use of inotropes, particularly dopamine and dobutamine, to treat very low birth weight infants with cardiac instability and neonatal postoperative cardiac patients. The cardiology group identified key issues that must be considered when designing studies of inotropic agents in preterm infants and proposed 2 clinical-trial designs: (1) a placebo-controlled trial with rescue for symptomatic infants; and (2) a targeted-blood pressure study. The first trial design would answer questions concerning efficacy of treatment with inotropic agents in this population. The second trial design would address concerns related to the lack of knowledge on normal blood pressure ranges in this population. The group identified specific design elements that would need to be addressed for the complicated trial design to study inotropic agents in neonates.

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The views presented in this article do not necessarily reflect those of the Food and Drug Administration (FDA). This article reflects discussions of designing clinical trials in newborns and should not be construed as an agreement or guidance from the FDA. Drug development and clinical-trial design must be discussed with the relevant review division within the FDA.

#### Key Words

hypotension, inotropic agents, neonatal blood pressure, dopamine, dobutamine

#### Abbreviations

VLBW—very low birth weight  
IVH—intraventricular hemorrhage  
PVL—periventricular leukomalacia

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FEW ASPECTS OF neonatal care have generated more controversy than those surrounding the appropriate determination of adequate tissue perfusion and the best approach to treatment of perceived abnormalities in blood pressure. Although up to half of all very low birth weight (VLBW) neonates admitted to NICUs receive treatment for “low blood pressure,”<sup>1</sup> there is no consensus regarding the actual definition of hypotension in the neonate. The decision to treat neonates for hypotension is usually based on data from studies that describe expected blood pressure ranges. Although numerous studies have detailed normative values for blood pressure on the basis of weight or gestational age as well as postnatal age,<sup>2-20</sup> the normal physiologic blood pressure range that ensures adequate organ perfusion is unknown. In addition, the reported “normal” blood pressure ranges may be influenced by management styles in a given institution.

The preterm neonate is uniquely ill-equipped to handle the cardiovascular changes that occur in the perinatal period and the demands imposed by illnesses in the first month after birth. An immature myocardium, the sudden presence of high vascular resistance, shunts through fetal channels, cytokine release causing vasodilatation, and the impact of positive-pressure ventilation on venous return and cardiac output can all contribute to inadequate systemic perfusion. Although there often may be several physiologic maladaptations occurring at once, several authors have proposed that hypotension in preterm and sick term infants is most often primarily a result of poor peripheral vasoregulation, with myocardial dysfunction or absolute volume depletion being less often the major cause.<sup>21-24</sup> A number of therapeutic maneuvers are commonly used in an attempt to correct systemic hypotension in the neonate, including volume expansion, inotropic agents, and corticosteroids. Although there is a paucity of research on the cardiovascular response to these commonly used agents in neonates, among the commonly used inotropic drugs dopamine has been shown to be more effective than dobutamine in raising blood pressure in the neonate.<sup>25-29</sup> However, several authors have questioned the efficacy of increasing systemic vascular resistance (eg, with dopamine) in the face of hypotension because the potential increase in afterload may reduce cardiac output and systemic flow.<sup>30</sup> Because peripheral resistance is an important determinant of organ blood flow, vasopressor agents such as dopamine might improve blood pressure without improving flow or ultimately improving outcome.<sup>28</sup>

In addition to the lack of information on what an adequate blood pressure for a neonate is and on how best to raise a perceived low blood pressure, there is no direct and prospectively collected information available on the result of treatment of a low blood pressure on neonatal morbidity and mortality. It has not been dem-

onstrated clearly that bringing systemic blood pressure to a normal range will improve outcome.<sup>31</sup> Despite the lack of definitive data, however, several lines of indirect evidence, including clinical observations, suggest that there is a direct relationship between low or fluctuating blood pressure and central nervous system injury in preterm neonates. Miall-Allen et al<sup>32</sup> demonstrated a highly significant relationship between a mean blood pressure of <30 mm Hg and intraventricular hemorrhage (IVH) in neonates born at 26 to 30 weeks' gestation. At least 2 additional studies have identified an association between IVH and low mean blood pressure.<sup>2,33</sup> A recent retrospective study<sup>5</sup> found no association among mean blood pressure, death, IVH, periventricular leukomalacia (PVL), or retinopathy of prematurity. However, certain characteristics of mean blood pressure (minimum low, maximum high, and highly variable levels) were all associated with IVH. Other authors have identified a relationship between significant fluctuations in blood pressure and IVH.<sup>2,34,35</sup> Goldstein et al<sup>36</sup> found that hypotension in VLBW neonates was an independent predictor of poor cognitive, motor, and neurologic outcomes at 6 and 24 months of age.

Although there does seem to be a relationship between hypotension and central nervous system injury, some authors have not found a correlation between blood pressure and cerebral blood flow and have questioned whether low blood pressure is only a marker for illness severity and not a primary determinant of outcome.<sup>37</sup> Complicating this issue further is the finding that, because systemic perfusion is the function of blood flow and systemic vascular resistance, blood pressure may well not always accurately reflect the status of organ blood flow in the infant.<sup>30</sup> More information is needed on the relationship between blood pressure and systemic blood flow (tissue oxygenation) and between systemic blood flow and morbidity and mortality.

In contrast to the widely held belief that normal systemic blood pressure indicates satisfactory cardiac output, studies have shown that in preterm neonates the 2 variables may be poorly correlated. It is possible that blood pressure is not the best target to manipulate to ensure tissue oxygenation.<sup>30,38</sup> However, in current practice, it is the primary measure used because of the ease of continuous monitoring of this parameter. In contrast to intensive care provided for older patients for whom direct cardiac output measurements are routine, such measures are not routinely available in neonatal intensive care. Even if these measures were readily available, interpretation would be difficult because of the frequent presence of atrial and ductal shunts. In the young neonate, assuming that ventricular output is an accurate measure of systemic blood flow is frequently incorrect.<sup>39</sup> This is particularly true in the preterm neonate for whom shunts are often directed from the systemic to the pulmonary circulation and may be large. For instance, it

has been demonstrated that using right ventricular or left ventricular output can overestimate systemic blood flow by  $\geq 100\%$  in these neonates.<sup>39</sup> Optimal management of neonatal hypotension might then require concurrent monitoring of blood pressure, cardiac output, and organ blood flow at the bedside, which is an approach that, unfortunately, is currently unrealistic in most NICUs.

Although there are promising new techniques that may provide information regarding organ blood flow, these techniques are not yet well-validated and not widely used, but they deserve additional study. In particular, measures of superior vena cava flow may prove to be a valid indicator of cerebral blood flow.<sup>39</sup> Superior vena cava flow is reported to reflect global flow to the upper body and brain, circumventing the confounding factor of intracardiac shunts (which renders ventricular output an inaccurate measure of organ blood flow in the early postnatal period).<sup>38,39</sup> It is important to note that low superior vena cava flow was shown by this group of investigators to be strongly associated with subsequent IVH<sup>40,41</sup> and to be a better predictor of IVH than mean blood pressure.<sup>42</sup> Similarly, near-infrared spectroscopy may be another useful measure of cerebral perfusion.<sup>43,44</sup>

Regardless of the controversy around these issues and the paucity of data, it is widely accepted by clinicians that early and aggressive treatment of hypotension (however defined) leads to improved neurologic outcome and survival in the neonate. Because of these complexities, the cardiology group addressed many study-design issues.

### STUDY-DESIGN ISSUES

The cardiology group identified the following key issues that must be considered when designing studies of inotropic agents in preterm infants.

- The cause of cardiovascular instability in VLBW infants is not fully understood and can be multifactorial, including factors such as poor peripheral vasoregulation, poor ventricular function (immature myocardium), transitional shunts, and acute blood loss.
- Definitive data for normative values for hemodynamic measures in VLBW infants are lacking. Information is not available on what constitutes adequate blood pressure for neonates, especially VLBW infants.
- Most measures of cardiovascular instability (eg, cardiac output) have not been validated in neonates, have limited availability, or may not be reliable, because of intracardiac shunting, or feasible, because of small patient size (eg, pulmonary arterial catheterization). As a consequence, blood pressure, along with urine output, acidosis, and capillary refill, remains one of the major parameters to follow. However, whether blood pressure reflects cardiac output and adequate tissue perfusion is unclear.

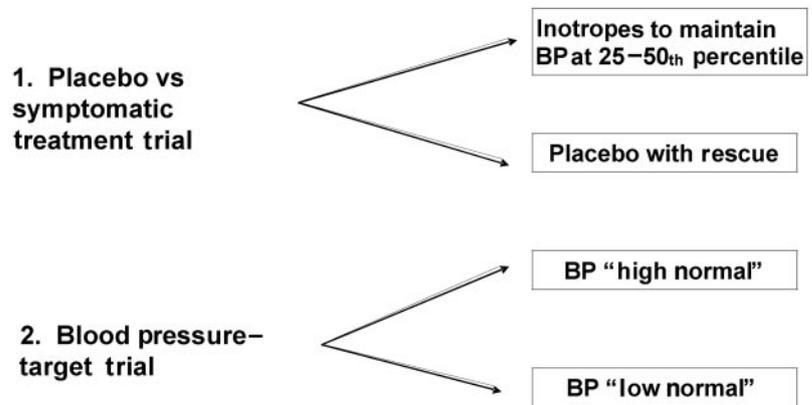
- Necrotizing enterocolitis, IVH, retinopathy of prematurity, neurodevelopmental outcome, and death are clinically relevant outcomes that reflect cardiovascular instability and end-organ injury.
- None of the current treatments for hypotension, including inotropic agents (eg, dopamine, dobutamine), have been well-studied in the VLBW population. Safety and efficacy studies in this group are lacking. Thus, labeling for the use of inotropes as therapeutic agents is inadequate.
- Research data are lacking on the cardiovascular response to commonly used therapies, including inotropic agents. Although dopamine and dobutamine are commonly used, studies of treatment with both drugs are needed to answer important questions. Results from small trials indicate that dopamine is more effective than dobutamine in improving blood pressure. However, recent studies indicate that dobutamine improves cardiac output as measured by superior vena cava flow and may improve end-organ perfusion, although dobutamine does not have as great an effect on blood pressure as that achieved by dopamine.
- Some data suggest that hypotension (or fluctuations in blood pressure) is associated with IVH or PVL. Other data suggest that certain therapies for hypotension are associated with increased IVH/PVL via sudden fluctuations in blood pressure and cerebral blood flow in the face of poor cerebral vascular autoregulation.
- Data from randomized trials in adults show an association between treatment with vasoactive agents and unexpected adverse outcomes such as mortality.
- The key research questions are to determine what optimal blood pressures in these infants are, how to optimize hemodynamic treatments, and how to identify any associations between blood pressure or therapy for low blood pressure and IVH/PVL, necrotizing enterocolitis, mortality, and neurodevelopmental outcome.

### PROPOSED CLINICAL-TRIAL FRAMEWORK

The cardiology group proposed 2 clinical-trial designs: (1) a placebo-controlled trial with rescue for symptomatic infants; and (2) a targeted–blood pressure study (Fig 1). Many group members recommended that a placebo-controlled trial be conducted to answer the question concerning efficacy of treatment with inotropic agents in this population. In this study, infants would be randomly assigned to receive placebo versus selected inotropic therapy. If clinical decompensation occurred, rescue therapy would be specified. The major unresolved issue was feasibility and acceptance by a large group of neonatologists, given the widespread use of dopamine and dobutamine in combination throughout US NICUs. The second trial design, a blood pressure–target study, would

FIGURE 1

The 2 study designs recommended for consideration for study are (1) a placebo-controlled trial and (2) a targeted hemodynamic trial. Patients in the placebo-controlled trial would be randomly assigned to receive either placebo or selected inotropic agents. The targeted– blood pressure (BP) trial is designed as a preventive trial, with patients randomly assigned to either a low or high blood pressure target. Hypotension in these 2 groups would be treated with a selected inotropic agent.



address concerns related to the lack of knowledge on normal blood pressure ranges in this population. In the blood pressure–target study, infants would be randomly assigned to 1 of 2 target blood pressures and would receive infusions of selected inotropic agents to maintain the target blood pressure. The target would be based on published data on normative blood pressure. For the blood pressure–target study design, selecting the appropriate target for the upper range of blood pressure was unresolved. In both studies, if clinical decompensation occurred, rescue therapy would be specified. All infants would receive standard volume replacement before inotrope or placebo therapy. The role of rescue therapy and steroids, which are given empirically to treat presumed adrenocortical insufficiency in VLBW infants, is a problematic area for both study designs. The group concluded that the study of inotropic agents in neonates would require a complicated trial design that would need to address the elements listed in Table 1.

With either design, the primary recommended outcome was a composite outcome of survival without grade 3/4 IVH (by head ultrasound at 7 days) or PVL (by head ultrasound at 28 days or by MRI at 36 weeks' postconceptional age). Secondary outcome variables to be considered were the incidence of necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, long-term neurodevelopmental outcome at 2 years of age, and other physiologic measures of tissue perfusion (see Table 1). Dose and effective combination of drugs should also be considered.

### UNANSWERED STUDY-DESIGN QUESTIONS

The blood pressure–target trial proposed for studying premature neonates has the potential to address drug efficacy and the appropriate hemodynamic target (eg, higher versus lower blood pressure) on long-term outcomes. This approach would avoid the ethical issues associated with using a placebo as outlined in the placebo trial. However, including a placebo in the trial might allow a reduction in the estimated study size from 800 to 300 infants. The group hopes that its poll of

neonatologists will indicate whether these professionals would be interested in a placebo-controlled trial. The cardiology group was left with the following unanswered ethical questions about the study design.

- After discussion, consensus was reached that the “high normal blood pressure” target was too high and had the potential to cause harm. Lowering this target, however, may not allow enough discrimination (separation) between the “high normal” and “low normal” blood pressure groups.
- The issue of whether a placebo-controlled trial is ethical when therapy is well-accepted requires additional consideration. Performing a placebo-controlled study would be ideal, but equipoise may not exist among neonatologists.
- Obtaining informed consent will involve approaching distressed mothers in premature labor and obtaining consent, which will make the trial more difficult to perform.

### QUESTIONS FOR WORKSHOP PARTICIPANTS

The cardiology group concluded that it needed additional input from neonatologists regarding these study-design issues before it could finalize the framework of a clinical trial. The group decided to solicit input from other neonatal colleagues. As a first step, the group posed a set of questions to the workshop participants. Input from neonatologists in the audience addressed the following questions:

#### What Drug Do You Use First Line: Epinephrine, Dopamine, or Dobutamine?

Dopamine seemed to be used more commonly as a first-line drug than dobutamine. Most of the workshop participants thought that epinephrine would be an acceptable rescue drug. No one thought that epinephrine would not be acceptable as a rescue drug.

**TABLE 1 Framework for the Study of Inotropes in Preterm Infants With Cardiac Instability**

Hypotheses	The following hypotheses should be studied Study 1: treating hypotension in neonates prevents adverse outcomes Study 2: preventing hypotension is protective
Pilot study	A pilot study in 1 or 2 centers would be needed to work out practical issues (eg, bedside monitoring, compliance and acceptance of titration scheme, and finalization the design)
Study population	Premature infants with a birth weight of 500–1000 g
Enrollment	Prenatal recruitment and enrollment of infants at birth would be essential because the trial would be preventive (ie, prevent hypotension in 1 group)
Procedures	An arterial line would be needed to measure blood pressure
Exclusion criteria	The work group proposed the following exclusion criteria Severe congenital anomaly Congenital heart diseases (except patent ductus arteriosus) identified by echocardiography Small for gestational age or intrauterine growth retardation
Primary outcome	The primary outcome would be the combined end point of mortality or a severe neurological outcome (IVH at day 7 or PVL at day 28 or discharge)
Secondary outcomes	The following indicators of end-organ perfusion damage would be secondary outcomes Necrotizing enterocolitis Retinopathy of prematurity Bronchopulmonary dysplasia Long-term neurodevelopmental outcomes (at 2 y) Other adverse events that could be caused by the drugs (eg, arrhythmia, hypertension, seizures, hormonal effects) Measures of organ perfusion (eg, superior vena cava flow, near-infrared spectroscopy)

### Would You Use Hydrocortisone to Treat Refractory Hypotension?

Many neonatologists would use hydrocortisone to treat refractory hypotension. About half of the responders would be comfortable following a rescue protocol that included hydrocortisone treatment.

### Would You Perform a Placebo-Controlled Trial in This Setting if Rescue Occurred With a Blood Pressure of <20 mm Hg (500–750 g)?

Participants were nearly evenly divided regarding whether they would be willing to perform a placebo-controlled trial that would randomly assign treatment with saline versus dopamine or dobutamine.

### Would You Conduct a Trial That Used Clinical Signs Only (eg, Poor Capillary Refill, Oliguria, Acidosis) as the Determining Factor for Study Entry With No Use of an Arterial Line/Blood Pressure Measurement?

More neonatologists than anticipated indicated that they would feel comfortable with a clinical-signs-only trial design. Many participants were undecided on this issue.

### Would You Allow Blood Pressure in 500- to 750-g Infants to Drop Below 20 mm Hg Before Starting a Rescue Drug?

Few neonatologists would allow blood pressure to drop to this level. A sizable number of participants were undecided on this issue.

### FUTURE DIRECTIONS

The cardiology group plans to send a questionnaire to members of the National Institute of Child Health and Development Neonatal Network and other large organized neonatal study groups such as members of the Perinatal Section of the American Academy of Pediatrics. After receiving input, the group will determine which clinical-trial framework it will recommend.

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