Summary Proceedings From the Cardiology Group on Postoperative Cardiac Dysfunction

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ABSTRACT

As many as one third of the 35 000 to 40 000 infants born in the United States each year with significant congenital heart defects require surgery before the first year of life. Intraoperative support techniques, including cardiopulmonary bypass, can precipitate a complex, systemic inflammatory response that impairs the function of multiple organs and results in more hemodynamic instability and early morbidity in newborns than in older infants and children. Vasoactive agents are routinely used in the postoperative management of these patients either to treat or prevent hemodynamic instability and low cardiac output. However, the effectiveness of vasoactive agents used either individually or in combination in achieving specific therapeutic goals such as maintenance of a minimum cardiac index or arteriovenous oxygen saturation difference has not been systematically evaluated in preterm and term neonates. In addition, there are insufficient safety data for these agents in preterm and term neonates, both as individual agents and in combination. This article proposes a framework for developing prospective clinical studies to determine the efficacy of different vasoactive agents to promote adequate cardiac output and hemodynamic stability after neonatal cardiac surgery. The framework provides an overview of the issues relevant to the design of prospective clinical studies of vasoactive agents in the newborn patient population undergoing cardiac surgery. The issues identified by the cardiology group illustrate the difficulty of designing and executing clinical trials in vulnerable pediatric populations with limited numbers of patients, especially when standard practice is widely believed to be beneficial despite the lack of rigorous data to support such practice.
BACKGROUND

Every year in the United States, 35,000 to 40,000 infants are born with significant congenital heart defects.1 As many as one third of these newborns require surgery during the first year of life. Intraoperative support techniques, including CPB, aortic cross-clamping, and deep hypothermic circulatory arrest, can precipitate a complex systemic inflammatory response that impairs the function of multiple organs2–4 and results in more hemodynamic instability and early morbidity in newborns than in older infants and children.3,5–7 Hemodynamic instability may cause variable systemic blood pressures, abnormally high heart rates or dysrhythmias,8 poor urine output, and decreased perfusion. If persistent, such instability can lead to a low cardiac output state with poor oxygen delivery, as manifested by low mixed venous oxygen saturation, elevated serum lactate, and metabolic acidosis. Multiple clinical studies beginning in the 1970s have associated early postoperative morbidity and mortality with low cardiac output in pediatric patients.3,5,9,10

The constellation of hemodynamic instability, low mixed venous saturation, elevated serum lactate, and metabolic acidosis is referred to as low cardiac output syndrome.11 Pharmacologic agents with inotropic properties (eg, the catecholamines, dopamine, and epinephrine) and vasodilatory properties (eg, the nitric-oxide donor, nitroprusside) are used in most PICUs in an effort to treat or prevent low cardiac output syndrome in postoperative cardiac patients.12 Inotropes improve cardiac output by increasing myocardial contractility and heart rate. Inodilators (agents such as the phosphodiesterase inhibitor milrinone) have vasodilatory as well as inotropic properties. Vasodilation can improve cardiac output by lowering systemic vascular resistance. Dopamine seems to be one of the most common inotropic agents used to treat postoperative cardiac neonates, but milrinone, epinephrine, dobutamine, calcium, and occasionally norepinephrine are used as well.

Because inotropes can improve postoperative hemodynamics, and because better hemodynamics have been associated with improved clinical outcomes, most cardiac surgeons, cardiologists, and intensivists believe that inotropes should be used routinely. However, the effectiveness of vasoactive agents used either individually or in combination in achieving specific therapeutic goals such as maintenance of a minimum cardiac index or arteriovenous oxygen-saturation difference has not been systematically evaluated in preterm and term neonates. The variability in choice of agents is due in part to the lack of sound data evaluating the effects of these agents on clinical outcomes. Furthermore, there are insufficient safety data for these agents in preterm and term neonates, both as individual agents and in combination.

STUDY-DESIGN ISSUES

Here we propose a framework for developing prospective clinical studies to determine the efficacy of different vasoactive agents to promote adequate cardiac output and hemodynamic stability after neonatal cardiac surgery. These studies should be conducted in preterm and term neonates with congenital heart defects who require cardiac surgery with CPB.

Many of the same uncertainties and complexities of defining and treating cardiovascular instability in the extremely low birth weight population exist for postoperative preterm and term neonates with congenital heart disease (see “The Newborn Drug Development Initiative Workshop I: Summary Proceedings From the Cardiology Group on Cardiovascular Instability in Preterm Infants” [page S34]). As for the extremely low birth weight neonates, simply increasing the systemic blood pressure to a specified target range does not guarantee that tissue oxygen delivery will be improved. For example, a neonate who has marked vasoconstriction may have a significantly higher systemic blood pressure but lower cardiac output and tissue oxygen delivery compared with a vasodilated and mildly hypotensive patient of the same gestational age.

However, there are also important differences in these subpopulations. First, it is rare for newborns weighing <1.0 to 1.2 kg to undergo cardiac surgery with CPB.13 Most preterm neonates undergoing cardiac surgery are >2.0 kg and thus significantly less premature than the newborns proposed for study in the framework on cardiovascular instability in preterm infants. Second, when low systemic blood pressure occurs in neonates early after cardiac surgery, it is frequently a result of myocardial dysfunction as opposed to the problems more commonly experienced by low birth weight neonates such as vasodilation associated with sepsis,14 respiratory distress syndrome, necrotizing enterocolitis, and intracranial hemorrhage.15 Myocardial performance can be impaired because of inflammation and transient myocardial edema related to CPB.4 Another important cause of low systemic blood pressure after neonatal CPB sur-
Another pragmatic issue that will affect scientific success is the number of patients eligible to be studied. This will be a particular problem for studies of preterm neonates undergoing cardiac surgery with CPB, but it is also an important consideration for studies of term neonates. For both populations, it is likely that a multicenter approach will be required.

Selection of a primary end point is one of the most important scientific decisions to be made when designing one of these studies. Mortality is considered the optimal end point for many clinical trials. In large pediatric cardiac centers in North America, however, postoperative mortality after complete repair of many congenital heart defects in neonates is currently <5%. Therefore, if a general neonatal cardiac surgery population is studied, enrolling sufficient patients to achieve adequate statistical power using mortality as the primary efficacy end point will be problematic, even in multicenter studies. In contrast, early mortality after initial palliation of the complex single ventricle lesion hypoplastic left heart syndrome using the modified Norwood procedure is ~10% to 15% in larger centers that are experienced with this procedure. Thus, designating mortality as a primary end point in studies of these patients may be feasible. It is likely to be more realistic, however, to identify efficacy end points other than mortality that will allow for a useful comparison between agents. Avoiding serious morbidity is a clinically relevant outcome that also often meets criteria used by the Food and Drug Administration (FDA) in considering labeling changes.

Examples of this type of end point in neonatal trials include evaluating the incidence of necrotizing enterocolitis, intracranial hemorrhage, or renal failure. Another strategy is to use a composite end point, combining mortality with ≥1 measures of morbidity or toxicity. The choice of a composite end point can complicate statistical analysis and interpretation of the results but should be seriously considered when small patient numbers are an issue. Regardless of the end point(s) chosen, a clinically relevant effect size will need to be determined.

- The effect of most of the variation in patient populations is accounted for by randomization, which should result in balanced study arms. However, it may be desirable to consider stratification of the study populations by ≥1 variables. The advantage of stratification is that the interpretation of results is more robust; however, a significant disadvantage is that stratification can result in small numbers in each stratum, thus requiring a larger sample size to ensure adequate power. For multicenter studies such as the ones proposed here in which the medical and surgical treatment regimens vary by center and cannot be easily standardized, stratifying by clinical center is desirable and likely worth the cost in sample size. Stratification by other variables such as cardiac diagnosis may not be feasible but should be considered in initial discussions of study design.

- Clinical studies of vasoactive agents in neonates will be complicated by a number of confounding factors. As noted, randomization is designed to minimize the impact of such factors, but we anticipate that the following comorbid conditions or preoperative treatments could confound the analysis of the data obtained in any clinical trial, thus making interpretation of the data on drug efficacy, safety, and dosing more difficult. Each of these would have to be considered in developing a final trial design and statistical plan.

- prooperative use of vasoactive agents such as prostaglandin E1;
- aspects of prooperative cardiac performance likely to affect postoperative cardiac function (eg, degree of atrioventricular valve regurgitation in single-ventricle patients);
- hypocalcemia requiring ongoing calcium-replacement therapy because calcium has inotropic properties (eg, patients with hypocalcemia caused by Di-George syndrome);
- unintended residual structural cardiac lesions;
- significant postoperative blood loss or chest-tube drainage that reduces intravascular volume and impairs preload;

- Although all trials must be scientifically sound, pragmatic issues have to be considered at the outset. It is important to understand local practice patterns, including where these neonates receive postoperative care (in a cardiac unit, general pediatric unit, or NICU) and who is responsible for directing their management. Knowledge of these practice patterns will provide essential information about who needs to be included in protocol development and whose support is required to ensure success of the study.

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glucocorticoid or thyroid hormone supplementation for cortisol or thyroid hormone deficiency (both cortisol and thyroid hormone have potential inotropic effects)24,25; and
- significant postoperative infection (although uncommon, such infections can affect cardiac output).

Another key scientific decision in designing a trial is selection of the study agent(s). This decision will be affected significantly by local practice patterns and the degree to which clinicians have equipoise about studying specific agents. Dopamine and dobutamine are in widespread use, with clinical “true belief” in their efficacy. It is unlikely that a placebo-controlled study of either of these agents, however desirable scientifically, would be embraced by clinicians. Publication of the results of the Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics (PRIMACORP) trial26 has led to widespread use of milrinone to reduce low cardiac output syndrome after cardiac surgery in pediatric patients of all ages, but it has not been evaluated yet in preterm neonates or in a large number of term neonates. Similar to studies with dopamine and dobutamine, we expect that many clinicians would hesitate to enroll their patients into a randomized, placebo-controlled trial of milrinone. In contrast, arginine vasopressin, otherwise known as antidiuretic hormone and a potent vasoconstrictor, has been used postoperatively to support blood pressure in only a small number of pediatric cardiac centers.27 Based on the hemodynamic benefits demonstrated in adults with congestive heart failure and elevated pulmonary capillary wedge pressures,28,29 human brain natriuretic peptide (BNP; trade name Natrecor) is being used in increasing numbers of pediatric patients. BNP is not an inotrope but rather improves cardiac output by enhancing myocardial relaxation, improving cardiac filling, and promoting peripheral vasodilation. Both arginine vasopressin and BNP are newer candidates for the types of prospective studies of vasoactive agents proposed in this framework.

Measurement of cardiac output will be an important component of any study undertaken of vasoactive agents in neonates with congenital heart defects. Cardiac output is not likely to be accepted as an adequate primary end point to support labeling changes by the FDA, but it could serve as an important secondary end point. A variety of invasive and noninvasive methods exist to assess systemic cardiac output in postoperative neonates, but all available methods have technical limitations. Knowledge of these limitations should be included in the study design of future trials, and attempts should be made to evaluate new techniques or measurements to determine cardiac output as part of these trials.

### PROPOSED CLINICAL-TRIAL FRAMEWORK

#### Study Groups

We propose that neonates undergoing CPB surgery for congenital cardiovascular defects be divided into study groups on the basis of gestational age and maturity because of expected differences in cardiovascular function and physiology as well as responses to vasoactive agents between preterm and term newborns.26,30 For example, the function and tissue-specific density of adrenergic receptors vary by gestational age and postnatal maturity.30,31 In addition, dosing ranges are different in preterm compared with term neonates.32,33 In many surgical studies, the patient population is defined by weight as opposed to maturity. Because physiologic parameters are correlated more with maturity than weight, it will be important to account for the degree of prematurity. The amount of time that elapses between birth and surgery will need to be accounted for as well, because developmental maturation continues to occur in the first month of life. Maturational differences could significantly affect the response of patients to surgery, the efficacy of other postoperative therapies, the pace of postoperative recovery, and the incidence of adverse events.

The standard definition of a preterm neonate is one who is born at <37 weeks’ gestation. However, biological differences that may be important for the proposed studies might be present at <34 to 35 weeks’ gestation. Defining prematurity for purposes of the proposed studies will require not only a careful review of the available literature on maturation of cardiovascular physiology but also considerations of optimal sample size for the end points chosen.

#### Study Population and Sample-Size Considerations

The study population for any trial should be as homogenous as possible, but the variability in congenital cardiac malformations and in local clinical practice will make homogeneity difficult to achieve. The desirability of stratifying by clinical center has been discussed previously. The following are other issues that a protocol committee developing the final trial design should consider.

#### Selection of Primary End Point

We have discussed the importance and difficulty of choosing a primary end point for these proposed clinical trials in the preceding section (see “Study-Design Issues”). As noted, it may be necessary to develop a primary end point other than early postoperative mortality for neonates who are to undergo complete repair versus those who will have complex palliative surgery. An accurate preoperative cardiac diagnosis and a detailed knowledge of the mortality and morbidity risks associated with specific cardiac diagnoses will be necessary to assign the most appropriate primary end point for the...
study populations. In “Summary and Next Steps,” we recommend one strategy for developing primary end points through the recruitment of experts in the field of pediatric cardiac intensive care.

Potential Secondary End Points
When the protocol is developed, we recommend that consideration be given to including ≥1 of the following as secondary end points to provide more detail about the postoperative clinical characteristics of the study population:

- duration of delayed sternal closure;
- duration of mechanical ventilation;
- duration of intensive care stay;
- duration of hospital stay after cardiac surgery;
- mortality beyond the 30th postoperative day;
- blood lactate levels and mixed venous oxygen-saturation measurements;
- creatinine clearance;
- BNP levels;
- need for additional vasoactive agents to support cardiac output;
- noninvasive measurements of cerebral blood flow; or
- neurodevelopmental assessment at 1 to 2 years of age.

Randomization Scheme
Vasoactive agents are typically started in the operating room at the completion of neonatal surgery, either while the patient is being weaned off of CPB or soon thereafter. Therefore, randomization should occur immediately before the operation or in the operating room. Each approach has advantages and disadvantages that should be weighed. Only those patients for whom vasoactive agents are clinically indicated would be enrolled into a study.

Inclusion and Exclusion Criteria
When determining inclusion and exclusion criteria, the goal is to include as many neonates in the study as possible while excluding those with conditions that could significantly affect the outcome but are independent of the intervention. Standard inclusion criteria that should be considered include presence of cardiac diagnosis requiring neonatal surgery, planned use of an infused vasoactive agent, and written informed consent of a parent or guardian. Exclusion criteria may be more difficult to formulate but could include severe cardiopulmonary collapse (which would need to be defined), need for emergency surgery that would preclude obtaining prior informed consent for the study, known infection, and a severe noncardiac congenital or chromosomal abnormality that is associated with a high risk of mortality or postoperative morbidity. Concerning the last criterion, a significant proportion of neonates with congenital heart defects also have noncardiac congenital anomalies, and as many as 35% of premature newborns with cardiac defects have noncardiac anomalies. Therefore, it will be important to include as many patients with less severe anomalies as possible to enroll representative populations. Therefore, patients with relatively common but less severe chromosomal anomalies such as trisomy 21 and chromosome 22q11 microdeletion (DiGeorge syndrome) should not be excluded.

Potential Trial Designs
These would be similar to the types proposed in the cardiology group’s cardiovascular instability in preterm infants framework and could include the following:

- Randomized trial of goal-directed management comparing the effectiveness of 2 inotropes in achieving the designated goal. For example, one could compare dopamine versus epinephrine (or dobutamine) in achieving a cardiac index of >2 L/min per m² or a systemic arteriovenous oxygen-saturation difference of <35%. This design would need to incorporate the concomitant use of other vasoactive agents such as inodilators or vasodilators. Similarly, a randomized trial of goal-directed management comparing the effectiveness of achieving the designated goal with 1 established vasodilator (eg, nitroprusside) in combination therapy with 1 of 2 different inotropic agents (eg, dopamine versus low-dose epinephrine) could be performed.

- Randomized trial of goal-directed management comparing the effectiveness of achieving the designated goal with a new inotropic agent versus an established inotropic agent. A similar design for evaluating a new inodilator or vasodilator in combination with 1 inotrope could be used.

- Randomized comparison trial of 1 vasodilator plus 1 inotrope versus another vasodilator plus the same inotrope (eg, BNP plus dopamine or low-dose epinephrine versus nitroprusside plus dopamine or low-dose epinephrine).

- Dose-ranging study of an individual new or established inotropic agent to enhance pharmacokinetic and/or pharmacodynamic data and to define or refine the hemodynamic effects of individual agents in the different patient populations (preterm versus term, repaired versus palliated). These studies are also recommended for the inodilators and vasodilators.

Study Structure
All of the studies described here would require a multicenter clinical-trial structure. The Pediatric Heart Network funded by the National Heart, Lung, and Blood Institute is the leading example.
Institute has demonstrated both the feasibility and the power of collaborative multicenter studies in patients with uncommon conditions. In general, this structure would include a data-coordinating center plus the participating clinical centers. Each study would be governed by a steering committee with representation from the data-coordinating center and each of the clinical centers. As for many phase III clinical trials, an independent data- and safety-monitoring board would be established to provide input on the protocol before its submission to local institutional review boards and to monitor data quality and patient safety on a regular basis during the trial. The data- and safety-monitoring board should be chaired by an individual with expertise in pediatric cardiology and clinical trials. Following standard procedures, the data- and safety-monitoring board should develop stopping rules based on achievement of a trial end point as well as stopping rules based on an excess of adverse events in one treatment arm.

Adverse Events
We anticipate that a significant proportion of the patients enrolled in these proposed trials will have important adverse events, in part because of their complex cardiac diagnoses and, in addition for some, because of superimposed prematurity. The protocols should have detailed adverse-event sections that define the approach to adverse events, including a list of occurrences that are to be considered study-related adverse events for the purposes of reporting to local institutional review boards, the data- and safety-monitoring board, the sponsor, and the FDA. Because of the nature of the study populations, consideration may be given to having a medical monitor affiliated with the data-coordinating center who will be responsible for the initial review of adverse events before the data- and safety-monitoring-board review. This is standard in large adult cardiovascular trials. The medical monitor would be a physician who has substantial expertise in pediatric cardiovascular disease and trials.

SUMMARY AND NEXT STEPS
The issues presented in this summary illustrate the difficulty of designing and executing clinical trials in vulnerable pediatric populations with limited numbers of patients, especially when standard practice is widely believed to be beneficial despite the lack of rigorous data to support such practice.

Steps that could be taken to refine this framework and move toward realization of a clinical trial protocol or protocols follow.

• As noted, one of the greatest challenges will be to identify and agree on efficacy end points other than mortality that will allow for a useful comparison between specific agents. These decisions will not only have implications for clinical practice but also for drug labeling, given the criteria used by the FDA to label an agent for use in pediatric patients. In addition, once these end points are chosen, a clinically relevant effect size will need to be determined. One mechanism for performing this task would be to convene experts in the field of pediatric cardiac intensive care to develop end points and decide on the relevant magnitude of effects so that a biostatistician could perform appropriate sample-size calculations. One group with specific expertise for these decisions is the Pediatric Cardiac Intensive Care Society (www.pcics.com). This group also could provide useful input for evaluating the aims and methods of the trials proposed in this framework, including issues such as scoring low cardiac output, managing intravascular volume status, and titrating the dose of study drug(s). We believe that obtaining input on efficacy end points and trial methods from a group of recognized experts would expedite the development and execution of these trials by the stakeholders.

• Distribute this summary document to the pediatric cardiology and pediatric cardiac surgery leadership of centers that perform clinical research in pediatric cardiovascular diseases to obtain feedback and an assessment of potential interest in trial participation. Starting points for this effort could include the National Heart, Lung, and Blood Institute–funded Pediatric Heart Network and participants in the recent Prophylactic Intravenous Use of Milrinone After Cardiac Operation in Pediatrics (PRIMACORP) trial, which evaluated milrinone use in pediatric cardiac surgical patients.

• Prepare and distribute a survey of vasoactive drug usage (focusing on the inotropes, inodilators, and vasodilators discussed here) to pediatric cardiac surgical centers to determine current strategy and practice. The results of such a survey could be used to determine which trial or trials would be likely to generate the most interest for the greatest number of centers.

• For any of the types of clinical trials proposed here, we recommend performing a pilot study with a limited number of subjects to determine the feasibility of the study before initiating a full-scale trial.

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