Preventing Brain Injury in Newborns With Congenital Heart Disease: Brain Imaging and Innovative Trial Designs

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Progress Review

Preventing Brain Injury in Newborns With Congenital Heart Disease

Brain Imaging and Innovative Trial Designs

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Background and Purpose—Newborns with congenital heart disease are at high risk for brain injury and adverse neurodevelopmental outcomes. MRI enables the objective determination of the severity of brain injury in critically ill newborns with congenital heart disease. We will rationalize the use of MRI as a surrogate for neurodevelopmental outcome and describe novel randomization techniques that can be used in trials in this population.

Methods—This article describes the evidence for the use of MRI and the link with neurodevelopmental outcome established in newborns. We also discuss the use of adaptive randomization techniques for future clinical trials in newborns with congenital heart disease. These strategies will be highlighted using an example.

Results—Brain injuries occur with high frequency in newborns with congenital heart disease. It is not until school age that the full extent of neurological sequelae becomes apparent and the rapid pace of innovation in neonatal cardiac surgery prevents timely evaluation of changes in care. MRI provides a timely, safe, and reliable outcome measure and has been extensively studied in newborns with other conditions in which the link between brain injury and neurodevelopmental outcome has been established. Clinical trials using MRI as an outcome measure as well as adaptive randomization can improve the efficiency of such trials.

Conclusions—Clinical trials of brain protection are urgently needed in newborns with congenital heart disease given the unacceptable frequency of brain injury in this population; MRI provides an early surrogate marker of long-term neurodevelopmental outcome and adaptive randomization can be used to improve the efficiency of these clinical trials. **(*Stroke*. 2009;40:327-332.)**

Key Words: brain injury ■ congenital heart disease ■ MRI ■ neurodevelopment ■ randomized, controlled trials

Experts have called for large clinical trials in the prevention of pediatric strokes based on the example set by pediatric oncology groups; oncology clinical trials have vastly improved the survival and outcomes of pediatric oncology survivors.[1] The incidence of stroke in the newborn is 20 per 100 000 live births and leads to a high risk of significant long-term neurological impairments for survivors,[2] including cerebral palsy,[3] cognitive deficits, visual disturbances, and epilepsy.[4] MRI is increasingly being used to detect stroke in the newborn. A number of imaging features of stroke are now recognized as predictors of adverse neurodevelopmental outcome.[3,5]

Newborns with congenital heart disease (CHD) are at increased risk for brain injury and adverse neurodevelopmental outcomes. High-resolution MRI and diffusion tensor imaging enable us to objectively determine the severity of brain injury in these newborns. Periventricular leukomalacia and neonatal strokes have both been reported to be the most significant lesions in terms of severity and incidence in infants that undergo CHD repair[6,7]; modifiable risk factors have been identified for both giving the hope that preventive strategies may be proposed. To illustrate advances in clinical trial design, this review focuses on the prevention of neonatal stroke. With the recent application of pre- and post-operative MRI in newborns with CHD, a number of preventable mechanisms for strokes in these high-risk newborns have been identified.[8] Given that the timing and mechanism of brain injury in newborns with CHD can now be identified, these infants can be studied to evaluate emerging strategies of brain protection.

Because the full extent of neuropsychological challenges do not become apparent until well into school age, today, it is necessary to wait 8 years or more to fully assess which newborns have the sequelae of acquired brain injury early in

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life.[9] As such, the pace of innovation in neonatal cardiac surgery outstrips the ability to evaluate the impact of new therapies on the brain. The quantification of brain injury overcomes this limitation and lays a unique and unprecedented foundation for testing new strategies for preventing or treating brain injury. Specifically, the availability of brain MRI as an early, predictive, and quantifiable outcome measure now opens a window for the implementation of new clinical trial methodology such as adaptive randomization; this technique requires a rapid ascertainment of the outcome.

This review addresses (1) the burden of neurodevelopmental impairments in children who had cardiac surgery as neonates; (2) how imaging studies provide a powerful prognostic tool for neurodevelopmental outcomes in high-risk newborns; and (3) novel clinical trial methods such as adaptive randomization can now be implemented with MRI as early measures of brain injury in newborns with CHD. Ultimately, the application of brain imaging and new methodologies for the evaluation of brain protection in these newborns will provide important lessons applicable to decreasing the burden of stroke in childhood.

Congenital Heart Disease Is Common and Associated With Adverse Outcomes

CHD refers to a variety of cardiac malformations present at birth and includes both cyanotic and acyanotic heart lesions. CHD occurs in 6 to 8 per 1000 live births and is a common cause of childhood morbidity. Up to 50% of these children require open heart surgery to correct their defect.[10,11] In Canada, 3518 newborns were affected with CHD in 1999 and the birth prevalence of CHD has increased steadily over the previous decade.[12] The economic cost associated with CHD in Canada exceeds $216 million annually and accounts for almost half of the economic burden of all birth defects.[13] A relatively homogenous type of cyanotic CHD that is amenable to early surgical correction is transposition of the great arteries (TGA). A recent study of 2 forms of cardiopulmonary bypass for the correction of TGA noted a neurological abnormality in up to 37% of the patients enrolled.[14,15] The deficits identified in this cohort of newborns with TGA persisted throughout childhood with significant detriment to school performance. By 8 years of age, children with surgical correction of TGA in the neonatal period had significantly lower scores than population means for fine motor skills, visual–spatial skills, and cognition, including memory, attention, and higher-order language skills.[16] In other cohorts, children with TGA were more likely to have abnormal neurological examination findings, learning disabilities, and behavioral disorders compared with population norms.[9,17–19]

Adverse neurodevelopmental outcomes are not restricted to newborns with TGA; motor and global developmental delays have been reported in children with multiple types of CHD.[14] For example, the incidence of major disabilities in survivors with hypoplastic left heart syndrome exceeds 60%.[20,21] The neurological basis for the high incidence of these developmental deficits in children with CHD is beginning to be understood with insight from neuroimaging. Together, these neurodevelopmental impairments result in significant detriment to the child, family, and society.

Opportunities for Intervention: Etiology of Neurodevelopmental Impairments

The timing of and mechanisms underlying neurodevelopmental deficits in children with CHD is multifactorial. Hypothesized etiologies include disturbances in brain metabolic function, brain injury, and abnormal brain development in addition to associated genetic conditions.[22] Given the degree of cyanosis and instability most CHD lesions present to the infant, it is not possible to delay definitive surgical correction to a time when the brain is less vulnerable. Initial studies of acquired brain injury focused on the operative period and cardiopulmonary bypass technique. Early surgical techniques for the correction of complex heart lesions during the neonatal period required a bloodless field and total circulatory arrest. Prolonged circulatory arrest time is identified as a major risk factor for subsequent neurodevelopmental impairments[9,14] in some reports, although not in others.[23] Long-term neurodevelopmental deficits in newborns with TGA are seen even after attempts to normalize cerebral blood flow during surgical correction of the heart lesion. In children repaired with full-flow cardiopulmonary bypass during the neonatal period, survivors at 9 years were more likely than best-friend controls to have lower full scale IQ scores, higher motor impairment scores, and lower social–behavioral competence scores.[24] Cardiopulmonary bypass itself may result in brain injury due to embolism, inflammation, and ischemia resulting in impaired delivery of energy substrates (oxygen and glucose).[25–31] Moreover, newborns have a pronounced decrease of mitochondrial oxygenation during induction of hypothermia and a delay in the recovery of the same after circulatory arrest.[28,29] Regional cerebral perfusion has been investigated as an alternative to deep hypothermic circulatory arrest. Some authors report no statistically significant differences in neurodevelopmental outcomes with this technique[32–34]; however, a high incidence of stroke has been reported.[35]

Other factors that have been associated with adverse neurodevelopmental outcomes include low gestational age, low birth weight, presence of a genetic syndrome, and high pre- and post-operative lactate.[23,36,37] Surprisingly, the complexity of the underlying cardiac lesion and the duration of cardiopulmonary bypass and deep hypothermic cardiac arrest were not associated with developmental outcomes.[21] Recently, it has been recognized that more than half of newborns with CHD have clinical evidence of neurological abnormalities on examination before surgery and that these abnormalities are a significant risk factor for later neurodevelopmental impairment.[18,36,38]

Role of Brain Imaging in Identifying Mechanism of Brain Injury

MRI studies of newborns with CHD have shown that up to 40% have preoperative brain injuries.[35,39] Postoperative MRI showed that an additional third of those studied acquired new injuries such that, overall, more than half of those studied had acquired brain lesions.[7,35,39] Stroke predominates as the brain lesion detected preoperatively, particularly in newborns with TGA.[8,35] The most common pattern of brain injury on postoperative MRI is white matter injury, particularly in neonates with single ventricle physiology and aortic arch

obstruction.[35,39] White matter injury is found in up to 55% of neonates who undergo cardiac surgery,[39] is found early in the postoperative course (6 to 14 days after surgery), and is more frequent in newborns with low cardiac output states postoperatively.[35,39]

Investigators are questioning the appropriateness of long-term follow-up as the only outcome to consider, because it is remote from the therapies under investigation. The pace of change with respect to surgical intervention is rapid, precluding long-term follow-up of patients enrolled in large randomized, controlled trials. Indeed, the perioperative management of patients with cardiac disease has changed dramatically in the past decade concurrent with a number of important changes in clinical management strategies: flow (circulatory arrest, low flow, full flow), cannulation (regional cerebral perfusion), pH management (alpha stat, pH stat), hemodilution/hematocrit, temperature (deep or moderate hypothermia, normal temperature), and ultrafiltration after cardiopulmonary bypass.

In 1990, Ferry et al[40] reported an incidence of overt postoperative neurological dysfunction of 25% in cardiac surgery survivors; by 2002, this incidence was reported as 2.3%.[41] Given the common occurrence of acquired brain injury detected by MRI in contemporary cohorts of newborns with CHD, we suspect that overt neurological dysfunction in the immediate postoperative period is not a reliable indicator of brain injury or future neurodevelopmental impairment. Despite this, the widespread acceptance of new practices or interventions by the clinical community often precedes the availability of long-term outcomes.[16,42–44]

There is speculation that neuroimaging may be a more useful tool to provide early prognostic information related to longer-term outcomes. In addition, there needs to be efforts to improve the efficiency of trials related to CHD and neurodevelopmental outcomes. Two aspects of trial design arise from these thoughts: Can MRI be a proxy measure for long-term outcomes? Can we determine therapeutic benefits faster than a regular randomized, controlled trial without losing power?

MRI as an Early Outcome Measure

Because changes on MRI correspond closely to histopathologic changes found on postmortem examination,[45–49] MRI can be applied in vivo to better anticipate the neurodevelopmental outcome after neonatal brain injury. A number of investigators have found that the severity and pattern of brain injury in the term newborns after a hypoxic–ischemic insult are strongly predictive of neurodevelopmental outcomes.[49–51] In the premature newborn, moderate to severe white matter injuries are highly predictive of cognitive and motor delays, cerebral palsy, and neurosensory impairments after adjustment for other measures of neonatal illness, including cranial ultrasound abnormalities.[49,52] Studies are ongoing in several centers to further link MRI appearance and neurodevelopmental outcome.

Historically, cranial ultrasound was used to diagnose strokes in newborns; however, Cowan et al[53] showed that these studies failed to diagnose up to 32% of neonatal strokes and were highly imprecise with respect to laterality and the site of lesion. Ultrasound correctly identified laterality and site in only 53% of cases when compared with MRI. Investigators have shown that the appearance of strokes on MRI is well correlated with neurological outcome.[5,54–57] In addition, the advent of MRI-compatible incubators, monitors, and ventilators makes MRI increasingly safe and feasible to obtain early in life in critically ill newborns. From these studies, it seems clear that MRI can provide objective, accessible, and early information on brain injuries such as global hypoxia–ischemia, stroke, and white matter injury, which can be used to inform neurodevelopmental prognosis in neonates who undergo cardiac surgery.

Future Directions: Adaptive Randomization

Determining "cause-and-effect" relationships can be difficult outside of the confines of a randomized, controlled trial. randomized, controlled trials can be time-consuming and expensive and conventional randomization may expose a large number of patients to less effective therapies. There are alternate methods of randomization, adaptive randomization, that can potentially reduce this and study duration. Because postoperative MRI provides immediate outcome data, we can use these randomization methods. Adaptive randomization allows probabilities to evolve in the course of a trial to favor the more successful therapy, thus decreasing the exposure of subjects to suboptimal therapy. Perhaps the best known of these strategies are "play-the-winner" rules such as that applied in the extracorporeal membrane oxygenation trial published by Bartlett et al,[58] which implied an "urn" model as follows.

Preceding randomization, balls labeled according to each of the 2 arms are placed in an urn. Randomization assignments were determined for each subject by drawing a ball at random from the urn and then replacing it. Each time, a final outcome was determined for a subject, if the outcome was a treatment success, a ball corresponding to the treatment given was added if the urn; otherwise, a ball corresponding to the other treatment is added. Thus, the number of balls (and thus the balance of probability) grows for the "winning" therapy.

Corresponding to the randomization, sequential decision rules are applied. In the extracorporeal membrane oxygenation trial,[58] the rule was to end randomization when 10 subjects had received extracorporeal membrane oxygenation or when 10 control subjects had died. The net result of the trial was that 10 subjects received extracorporeal membrane oxygenation therapy and lived with one only one subject assigned to control, who died. Unfortunately, the author's conclusion of efficacy for extracorporeal membrane oxygenation was greeted with much skepticism due to having only one control subject.

Another adaptive rule, "drop-the-loser," is aimed at avoiding such profound treatment imbalances. One version of this approach starts with one ball for each treatment type in the urn together with a "type 0" ball. As previously described, treatments are determined by drawing from the urn, but the ball is only returned to the urn once the subject's outcome is known to be a success. If a draw produces a "type 0" ball, that ball is replaced and one ball of each treatment type is added to the urn and the draw is repeated.

These techniques are less intuitive than conventional randomization and the analysis more challenging. Some authors have questioned the power of these techniques,[59,60] whereas others have provided power calculations and methods for sample size calculation.[61] In adaptive randomization, the observations are not independent of one another and standard regression approaches cannot be used. Inferences can be drawn based on a simple difference in outcome between the 2 groups (ie, treatment A versus treatment B) or by generating an odds ratio.

A final method of adaptive randomization is the use of Bayesian methods. Bayesian adaptive randomization marries the scientific ideal of conventional randomization and personal preferences for one treatment over another that may be incorrect. In clinical medicine, physicians have opinions regarding the most appropriate therapy based on numerous factors. Bayesian statistics allows for the incorporation of this information, in the form of prior probabilities, which are then modified by combining these probabilities with observed data to compute a posterior probability that is used to make statistical inferences.[62] Bayes' Law can be applied repeatedly using the posterior probability obtained after a given stage as the prior for the next stage, providing a framework for making decisions based on accumulating data during a clinical trial. Practically speaking, this can be implemented with a randomization program linked to a database such that the probabilities can be constantly updated. In this way, patients enrolled later in a trial benefit from the results of previous patients in the trial as the probability increases that they receive the more effective treatment.[63] It is extremely important, however, that the prior probabilities are carefully generated based on appropriate data and information. In addition, a "run-in" period of parallel randomization can be incorporated before Bayesian methods are used allowing for more accurate prior probabilities to be generated.

By way of example, we propose a trial that would use these methods. We want to determine whether the use of heparinization during balloon atrial septostomy for infants with TGA reduces the incidence of stroke as seen on MRI compared with placebo. MRI could be performed both pre- and postoperative balloon atrial septostomy. If conventional randomization were to be used for a trial of this nature, assuming a reduction in stroke of 50% with heparin use, 100 patients would need to be randomized; this would require many years of recruitment at multiple sites. Comparatively, with Bayesian methods, the sample size varies depending on the "success" rate of heparin, ie, the reduction in stroke as diagnosed by MRI allowing for the efficient recruitment of patients and limiting the study duration (Figure). Of note, the sample size never exceeds that required by conventional randomization (n=100). In addition, a trial such as this could also be used to further explore the correlation of MRI and longer-term developmental outcomes by including a follow-up component.

One concerning feature of these techniques is how the results can be used in the clinical arena to change practice. These trials inform the "probability" that the experimental intervention is effective. None of these methods allow for the calculation of a probability value. Although "probabilities" are much more intuitive than probability values in the clinical realm of decision-making, clinicians who are uncertain or skeptical of these techniques may question the validity of the results and be hesitant to incorporate changes into their practice. A concerted effort to make these techniques robust and appropriately used would have to be made to ensure effective and efficient knowledge translation of the findings.

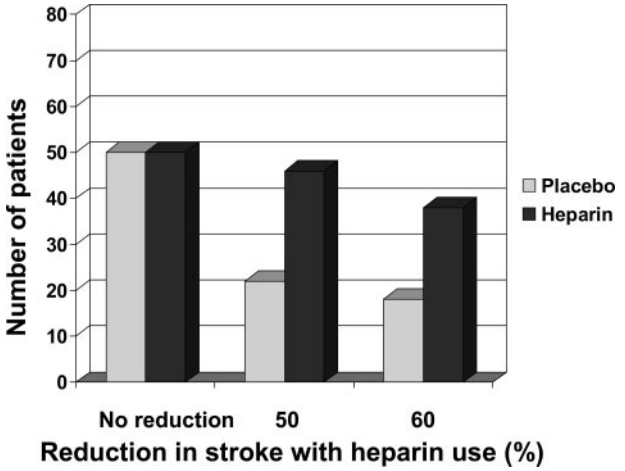

Figure. Total sample size necessary for a clinical trial designed using Bayesian randomization according to the reduction in stroke between heparin-treated and placebo groups.

From an ethical perspective, particularly in light of the high incidence of brain injury in newborns with CHD receiving standard care, adaptive randomization is appealing to clinicians caring for these newborns. They can feel that they are offering the best care for the infant while continuing to contribute to the scientific evidence.

Conclusions

Clinical trials of brain protection are urgently needed in newborns with CHD given the unacceptable frequency of brain injury in this population. Newborns with CHD account for a large proportion of potentially preventable pediatric strokes with the concomitant burden of disease. MRI of the brain and adaptive randomization are useful tools in trials that examine therapies related to CHD and the subsequent neurodevelopmental effects by optimally testing brain injury prevention strategies. With a concerted effort to apply adaptive randomization techniques appropriately using MRI as an early outcome of brain injury, effective and efficient knowledge translation of the findings from trials of brain protection in newborns with CHD should be possible avoiding the need to implement changes in care without vigorous evaluation.

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None.

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