

Association Between Method of Cerebral Protection During Neonatal Aortic Arch Surgery and Attention Deficit/Hyperactivity Disorder

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Background. Neonates undergoing repair of the aortic arch are at risk for adverse neurodevelopmental outcomes, including attention deficit/hyperactivity disorder (ADHD). The purpose of this study was to compare the effect of deep hypothermic circulatory arrest versus regional cerebral perfusion on the long-term outcome of ADHD.

Methods. This study is a cross-sectional observational study of ADHD in children who underwent neonatal aortic arch surgery. Attention Deficit/Hyperactivity Disorder-IV surveys were used to determine the prevalence of ADHD. Review of the medical records was performed to determine the primary method of cerebral protection and to extract related surgical variables.

Results. Surveys were sent to parents of 134 children, with 57 surveys completed (43%). The percentage of children classified as having ADHD was 44%. Children with a

diagnosis of interrupted aortic arch had the highest prevalence of ADHD (85%). Multivariate analysis demonstrated that interrupted aortic arch was associated with an increased ADHD inattention score ($p < 0.01$), and a decreased Child Health Questionnaire-50 psychosocial score ($p < 0.01$). Low Child Health Questionnaire-50 psychosocial summary scores are associated with increased behavioral problems and are lower in patients with ADHD.

Conclusions. Attention deficit/hyperactivity disorder is common after neonatal aortic arch surgery and may be primarily related to genetic predisposition. We found insufficient evidence to show that either deep hypothermic circulatory arrest or regional cerebral perfusion decreased the risk of ADHD.

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Methods of cerebral protection during infant aortic arch repair include either deep hypothermic circulatory arrest (DHCA), with complete interruption of cerebral blood flow, or regional cerebral perfusion (RCP). Both approaches may place patients at risk for cerebral oxygen deprivation, with an attendant risk of neurodevelopmental impairment. During the past decade, the primary neuroprotective strategy used in many congenital heart surgery centers has evolved away from DHCA and toward RCP [1]. Despite this shift, neurodevelopmental scores in children after complex neonatal cardiac surgery are still below the mean of the general population, especially in the area of motor development [2]. Short-term neurodevelopmental outcomes, as measured by the Bayley Mental Developmental Index and Psychomotor Development Index, may not correlate well with long-term outcomes that are important to children and their families, such as attention deficit/hyperactivity disorder (ADHD) [3]. Several recent studies indicate a potential association between congenital heart disease and an increased prevalence of ADHD [4–7]. Attention deficit/hyperactivity disorder may have a profound effect on children and their families [8]. Attention

deficit/hyperactivity disorder affects family dynamics, reduces scholastic achievement, and ultimately may limit success in the workplace. Many factors other than the surgical strategies used for neurologic protection may affect long-term neurodevelopmental outcomes and ADHD. However, it is important to understand the associations between potentially controllable surgical factors related to cerebral protection and the long-term outcomes that are important to children and their families.

Despite its widespread adoption, RCP has never been evaluated for its impact on the incidence of ADHD. Because previous studies using DHCA and RCP have primarily reported short-term neurodevelopmental outcomes, it is not clear whether there is an association between the approach to neuroprotection and the risk of long-term neurodevelopmental morbidity, such as ADHD. The purpose of this study is to compare circulatory arrest with regional low-flow cerebral perfusion during neonatal aortic arch surgery in a single center on the outcome of ADHD in children 5 to 16 years of age.

Material and Methods

Subjects

This study is a cross-sectional observational study of the prevalence of ADHD in a single-center surgical cohort of

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Abbreviations and Acronyms

ADHD	= attention deficit/hyperactivity disorder
ADHD-IV	= Attention Deficit/Hyperactivity Disorder Rating Scale IV
CHQ-50	= Child Health Questionnaire-50
DHCA	= deep hypothermic circulatory arrest
IAA	= interrupted aortic arch
RCP	= regional cerebral perfusion

children who underwent neonatal aortic arch surgery between July 1, 1995, and June 30, 2006. A review of the surgical records of the Medical University of South Carolina identified 216 children who underwent neonatal aortic arch surgery using either DHCA or RCP during this period. Surgical procedures included Norwood stage I, repair of interrupted aortic arch (IAA), and combined repair of aortic coarctation with ventricular septal defect. In our center, DHCA was the primary method of cerebral protection from 1995 to 1999, whereas RCP was the primary method from 2000 to 2006. Patients having DHCA or RCP as the primary method of neuroprotection were compared on the basis of ADHD classification and survey scores.

Data from patient medical records were extracted to determine the method of cerebral protection and perioperative risk factors. These included operative weight, year of surgery, known genetic syndromes, circulatory arrest time, regional cerebral perfusion time, lowest hematocrit, mean partial pressure of carbon dioxide, mean arterial pressure, and flow index during cooling. All genetic syndromes that tested positive including all testing for 22q11 deletion syndrome were recorded. Regional cerebral perfusion was carried out by means of the innominate artery at flow rates of 15 to 20 mL · kg⁻¹ · min⁻¹. Alpha blockade with phentolamine (0.1 mg/kg) was given during cooling and rewarming.

Attention Deficit/Hyperactivity Disorder Assessment

The ADHD Rating Scale-IV is a validated instrument for assessing the risk of ADHD in boys and girls aged 5 to 17 years. The scale is linked directly to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition diagnostic criteria for ADHD. The ADHD-IV rating scale has 18 scale items, which are based on the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition criteria. The survey results in three final scores: one for inattention, one for hyperactivity-impulsivity, and one combined score, which is the total of the other two scores. Raw scores are converted to percentiles based on the subject's age. The higher the percentile, the greater the risk of ADHD. In the validation study for the ADHD-IV survey, an inattention score greater than or equal to the 93rd percentile had the highest correlation with a diagnosis of ADHD [9].

The Child Health Questionnaire-50 (CHQ-50) quality-of-life instrument has been validated and normed for

children 5 to 18 years of age, and measures 14 psychosocial and physical concepts. The CHQ-50 summary scores combine results to derive an overall physical and psychosocial score, and identify key health conditions related to ADHD, such as attention, learning, and behavioral problems. The CHQ-50 has been validated in a population of children diagnosed with ADHD. Attention deficit/hyperactivity disorder is associated with a CHQ-50 psychosocial score of 37 or less. Low CHQ-50 psychosocial summary scores are associated with increased behavioral problems and are lower in patients with ADHD [10].

Study Design and Measurements

After approval by the institutional review board, a recruitment letter from the Children's Heart Program of South Carolina was sent with the surveys. The parents were asked to complete the ADHD-IV survey (home version) and the CHQ-50, as well as a questionnaire to determine whether a diagnosis and treatment of ADHD had been made. Children were assigned to the classification of ADHD if there was either a parent-reported diagnosis of ADHD or an ADHD-IV inattention score greater than or equal to the 93rd percentile. This criterion for the classification of ADHD was based on the optimal cutoff score reported for a diagnosis of ADHD. Because some children who were diagnosed and receiving medical treatment for ADHD may have had an ADHD-IV inattention score below the 93rd percentile threshold, children with a formal diagnosis of ADHD were also included in the overall prevalence rate. Additional evidence for the correct classification of children with ADHD in our study was determined by its association with the CHQ-50 psychosocial composite score.

Subjects were divided into three groups based on the method of cerebral protection. In group 1 (n = 21), the method was DHCA, whereas in group 2 (n = 24), RCP was the primary method (DHCA < 10 minutes). Group 3 (n = 12) had RCP and DHCA (DHCA > 10 minutes).

Statistical Methods

Descriptive statistics include median and interquartile range for skewed variables, mean ± standard deviation for other continuous variables, and frequency with percentage for categorical variables. The Kolmogorov-Smirnov test was used to determine normal distribution. Spearman's rank-order correlation was used to test the independent continuous variables. The Mann-Whitney *U* test was used for testing two independent categorical variables, and the Kruskal-Wallis test for independent samples with pairwise comparisons for testing more than two independent categorical variables. Variables in the univariate analysis with an unadjusted probability value of less than 0.05 were used as candidate predictors for multivariate modeling. All analyses were conducted using IBM SPSS Statistics for Windows, version 22 (IBM Corp, Armonk, NY).

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