The short term effects of cardiopulmonary bypass on neurologic function in children and young adults

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Received 21 May 2004; received in revised form 13 July 2004; accepted 15 August 2004; Available online 11 September 2004

Abstract

Objective: Cognitive deficits are common in adults following surgery utilizing cardiopulmonary bypass (CPB). A previous retrospective study suggested that surgical closure of an ASD in children was associated with neurologic injury, while transcather therapy was not. In a prospective study, we sought to determine whether neurologic deficits occur following repair of non-complex congenital heart lesions in school-age children and young adults.

Methods: Inclusion criteria were: age between 5 and 20 years, cardiac surgery utilizing CPB without deep hypothermic circulatory arrest, and no prior cardiac surgery. Patients underwent psychometric testing 1–3 days prior to surgery and re-evaluation 7–18 days after surgery. In order to determine the test/re-test effect an age-matched cohort of children undergoing transcather closure of ASD under general anesthesia was also evaluated. The primary outcome measures were verbal and picture memory. Additional psychometric tests included: computerized performance test (CPT) and Digit Span (DS). Forty-one patients were enrolled, 29 undergoing surgery with CPB and 12 controls. Surgical procedures included ASD closure (n = 13), VSD closure (n = 10), resection of sub-aortic stenosis (n = 3), mitral valvuloplasty (n = 3). Mild hypothermia was used in all cases. The mean duration of CPB was 54 ± 22 min.

Results: There was no significant difference in any of the psychometric test scores between subjects undergoing surgery with CPB or controls.

Conclusions: There are no marked adverse neurologic effects of CPB in school-age children and young adults undergoing non-complex open-heart surgery. These data are important in counseling patients and families and should be considered in the debate as to the relative merits of transcather versus open-heart repair of various heart lesions.

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Keywords: Cardiopulmonary bypass; Heart defects; Congenital

1. Introduction

Cardiopulmonary bypass (CPB) has become a standard, widely used, low-risk procedure that is employed in over 15,000 children in the United States each year. CPB, however, affects many organ systems, including the heart, lungs, kidneys and brain. Several recent studies have found that as many as 80% of adults who undergo heart surgery with CPB have neurologic deficits after surgery [1–3]. In these recent studies impairment of memory and attention have been noted most frequently. CPB is also used in the surgical repair of many congenital heart defects in children. Whether children undergoing surgery non-complex congenital heart surgery with CPB experience neurologic injury similar to the adult is unclear. One retrospective study suggested that children who had surgical closure versus catheter closure of atrial septal defects (ASDs) had lower scores on psychometric evaluation at intermediate follow-up [4]. In the present study, we sought to determine whether children demonstrate cognitive deficits after undergoing open-heart surgery with CPB.
2. Methods

A prospective observational study was carried out at the Children’s Healthcare of Atlanta at Egleston with the approval of the Institutional Review Board. Patients were eligible for enrollment if they were between 5 and 20 years of age, had no prior history of open-heart surgery, and were scheduled to undergo corrective cardiac surgery utilizing CPB, without deep hypothermic circulatory arrest. Exclusion criteria included: chronic cyanosis (room air utilizing CPB, without deep hypothermic circulatory arrest. Patients undergoing corrective cardiac surgery with CPB have demonstrated that specific neuropsychologic domains appear to be affected preferentially. Deficits have been documented in verbal memory and language comprehension, abstraction, attention and concentration. As such a battery of tests to examine similar domains was employed. Patients underwent psychometric testing before and after intervention, surgery or catheterization. The pre-procedure evaluation was performed the morning prior to surgery for the surgical cohort and on the morning prior to surgery for the control group. Follow-up studies were performed 7–18 days after intervention.

The primary outcome variable was picture and verbal memory. The present study focused on short term effects of CPB and children were tested and re-tested in a relatively short time-frame. As such it was necessary to design a battery of tests that would not be susceptible to significant re-testing effect. Therefore, to assess memory the subjects were randomly given either the Children’s Memory Scales (CMS) stories or the Wide-Range Assessment of Memory and Learning (WRAML) test. For post-procedure evaluation subjects were given the battery not administered pre-test evaluation only. The primary outcome variable was picture and verbal memory. The present study focused on short term effects of CPB and children were tested and re-tested in a relatively short time-frame. As such it was necessary to design a battery of tests that would not be susceptible to significant re-testing effect. Therefore, to assess memory the subjects were randomly given either the Children’s Memory Scales (CMS) stories or the Wide-Range Assessment of Memory and Learning (WRAML) test. For post-procedure evaluation subjects were given the battery not administered before the procedure. Such substitution is considered valid since the instruments have been shown to have excellent correlation and have both been referenced to normal pediatric populations [5]. The digit span sub-test of Stanford-Binet Intelligence Scale-IV was administered to assess attention. The computerized performance test (CPT) was also administered to assess attention and reflex time. The parents were asked to complete the Behavior Rating Inventory of Executive Function™ (BRIEF™). The BRIEF™ consists of a single rating form used by parents, teachers, and day care providers to rate a child’s executive functions within the context of his or her everyday environments—home and preschool. Each BRIEF questionnaire contains 86 items in eight nonoverlapping clinical scales. To assess whether the surgery group and control groups were comparable an abbreviated Wechsler Abbreviated Scale of Intelligence (WASI) was administered at the pre-test evaluation only.

3. Anesthetic and cardiopulmonary bypass management

3.1. Anesthetic management

Patients undergoing interventional procedures in the cardiac catheterization laboratory were premedicated with oral midazolam, 0.5 mg/kg. Anesthetic induction and maintenance consisted of an inhaled technique with nitrous oxide and either sevoflurane or isoflurane in oxygen. Nitrous oxide was discontinued during the right heart catheterization, and patients were ventilated at a FiO2 of 0.21. Patients were intubated prior to placement of the transeosophageal echocardiography probe. Post-procedure analgesia consisted of local infiltration of lidocaine at the femoral puncture site and intravenous ketorolac, 0.5 mg/kg. Supplemental oxygen was applied only until patients were fully aroused. Antibiotic prophylaxis consisted of cefazolin 50 mg/kg intravenously, once decision to proceed with device deployment was confirmed.

Patients undergoing operative closure of ASDs were similarly premedicated (midazolam 0.5 mg/kg). Anesthetic induction and maintenance were comparable except for the addition of fentanyl (10–15 mcg/kg total) and small doses of midazolam (1 or 2 mg) before CPB. They also received isoflurane during CPB and a propofol infusion after CPB until arrival in the intensive care unit (ICU). Patients were awakened and extubated on arrival to the ICU.

CPB blood gas management was by the alpha-stat method and a hematocrit of 30% was maintained, transfusing blood as needed. These patients were not actively cooled, but their temperatures were allowed to decrease passively during CPB. Average lowest temperature with this method was 34°C. All patients were rewarmed to 37°C prior to separation from CPB. Patients received methylprednisolone 30 mg/kg (maximum dose 1 g) and cefazolin 50 mg/kg (maximum dose 1.5 g) intravenously after anesthetic induction and mannitol 0.5 gm/kg and furosemide 2 mg/kg (maximum dose 20 mg) into the CPB circuit upon rewarming. No patients were treated with modified ultrafiltration. Twenty-five patients were managed with aortic cross-clamping and cardioplegia (JF and PK) and others (n=11) had ventricular fibrillation induced and no aortic occlusion (KK).

Patients undergoing resection of subaortic stenosis, were premedicated with meperidine 3 mg/kg, pentobarbital 4 mg/kg and atropine 0.02 mg/kg. Anesthetic management was similar to the above patients, except that these received more fentanyl (up to 50 mcg/kg) and no propofol. They were also not awakened and extubated immediately.
afterwards, but rather between 2 and 6 h later. CPB management was identical, except that all patients in this group underwent aortic cross-clamping and cardioplegia. This group also was assessed and monitored intraoperatively with transesophageal echocardiography, while the operative ASD patients were not.

3.2. Data collection and statistical analysis

Values are expressed as mean ± SD. Results of cognitive tests were analyzed by use of a two-tailed Student’s t-test. Unpaired t-test and Fisher Exact test were utilized to compare baseline characteristics of the two patient subgroups. To examine for a possible association between patient and procedure-related variables and changes in verbal or picture memory in the surgery cohort linear regression analysis was undertaken. Analysis was performed with STATA™ 6.0 (College Station, TX). Significance was determined at P-value of <0.05. All P-values are two-sided and confidence intervals are 95%.

4. Results

4.1. Patient population

The study group consisted of 29 patients who underwent surgery (Table 1) and 12 patients who had catheter closure of a secundum ASD. There was no significant difference between the two groups with respect to age or gender (Table 2). Both study groups were also similar with respect to pre-procedure evaluation of full-scale, verbal and performance IQ. There were no clinical neurologic complications noted for either patient group. The median duration of CPB for the surgery cohort was 46.5 min. (Table 3) The surgery patients had a mean length of mechanical ventilation of 6.9 ± 4.8 h. The median intensive care unit stay was 1 day (range, 1–4 days) and the median hospital stay was 4 days (range, 3–8 days). All of the patients undergoing transcatheter closure of ASD were discharged to home on day following the procedure.

On most of the standardized testing there was a trend toward higher scores on post-procedure evaluation. Changes in test scores ranged between −0.9 and +10.3 points and most likely represent increased familiarity with testing process, ‘re-testing effect’. When comparing the change in test scores between the two study groups there was no significant difference in any of the standardized tests of cognitive function (Figs. 1a and b, 2 and 3). There was a trend toward lower scores on evaluation of verbal memory in those patients who underwent surgical interventions (Fig. 1a). In the surgery patients, we also looked for associations between patient and procedure-related variables and changes in the primary outcome measures, verbal and picture memory. There was no significant association between age, duration of CPB, lowest nasopharyngeal temperature, lowest hematocrit, duration of mechanical ventilation, or length of stay with the primary outcome measures.

Parental perception of the child’s status also failed to demonstrate any differences between those patients undergoing surgical versus transcatheter interventions (Table 4). It is interesting to note that both parental ratings tended indicate lower scores than that noted by standardized testing administered by a neuropsychologist.

5. Discussion

CPB has been successfully utilized in the surgical correction of congenital heart disease for nearly 50 years. CPB allows for perfusion of vital organs by providing oxygenated blood via a mechanical pump. In children with relatively uncomplicated congenital heart disease—such as an ASD—the procedure is generally well tolerated, with a short duration of CPB, minimal perioperative morbidity and an increasingly shorter hospital stay [6]. The potential central nervous system effects of CPB are rarely considered in the risk-benefit decision analysis to undergo surgery; rather, the hemodynamic and anatomic effects of

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<th>Diagnosis and operative procedure</th>
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<tr>
<td>Diagnosis</td>
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<tr>
<td>Secundum ASD</td>
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<tr>
<td>Sinus Venosus ASD</td>
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<tr>
<td>Primum ASD</td>
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<tr>
<td>Perimembranous VSD</td>
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<tr>
<td>Sub-aortic membrane</td>
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<td>Mitral regurgitation</td>
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ASD, atrial septal defect; VSD, ventricular septal defect.
the unrepaired congenital heart disease generally lead the practitioners to recommend surgical correction. However, several studies have shown that cognitive abnormalities in adults following coronary artery bypass grafting and valve replacement performed with CPB [1–3, 7]. Embolic complications have been implicated in neurologic injury [8]. In addition, cardiovascular surgery with CPB leads to activation of a variety of inflammatory pathways [9]. Cerebral edema has been noted in post-operative neuroimaging of adults [10]. Lastly, hypoperfusion of the brain can lead to injury of watershed regions of the brain [11].

Standardized testing of adults before and after surgery using CPB has shown a high incidence of abnormalities of short-term memory, concentration, visual-spatial relationships and behavioral changes [1, 3]. Cognitive deficits have been reported in up to 80% of patients who have undergone coronary artery bypass graft surgery. Significant residual deficits can be detected in over 40% of these patients 5 years after surgery [1]. Less frequently, adults may have more profound neurologic sequelae, including stroke, coma and hemorrhage [3, 8]. The report of neurologic deficits among adults undergoing coronary artery surgery without CPB—so called ‘off-pump’ support—suggests that CPB may not be only the factor accounting for post-operative deficits [12]. The applicability of these adult findings to the pediatric population is difficult, given the high incidence of co-morbidities in adults, such as carotid artery disease and diabetes. It would stand to reason that cardiovascular surgical procedures that use CPB in school-age children might also result in cognitive deficits.

In recent years, a variety of non-surgical techniques to repair congenital heart disease such as trans-catheter closure of septal defects have been developed [13, 14]. A potential advantage of these non-surgical techniques is that the patient is not exposed to CPB. One retrospective study suggested that patients who underwent transcatheter closure of an ASD scored better than patients with an ASD who had undergone surgical repair on several standardized cognitive tests including Full-Scale IQ and Block Design [4]. This study attempted to control for a variety of factors including socioeconomic status and parental IQ. However, there were
several methodologic limitations to this study. Most importantly, patients were not tested before and after the procedures. Therefore, the difference in post-procedure test scores may have been related to pre-procedure factors. Nonetheless, this study and the literature from the adult population raised concern that school-age children undergoing surgery with CPB may suffer cognitive deficits.

More recently, Stavinoha and colleagues [15] undertook a study of pediatric patients undergoing surgical closure of a secundum ASD with pre- and post-cognitive testing. The primary outcome measure in this study was The Differential Ability Scales, which contains cognitive and achievement batteries for children aged 2.5 through 17 years. The authors reported [19].

In the present study, we also failed to demonstrate any significant cognitive deficits in school-aged children undergoing surgery with CPB. Unlike the patients described by Visconti et al. [4] who underwent repair at a mean age of 3 years, the mean age of surgery in our cohort was 7.5 years.

In addition, the group from Children’s Hospital Boston suggested that a low hematocrit, the mean in their study was 18.2%, may have contributed to neurologic deficits. At our institution the hematocrit is generally maintained at > 28%.

In addition, to subjects with ASDs the present study included patients with restrictive VSDs and sub-aortic membrane. Recognizing the limitations of small number of patients in each sub-group, we found no association between the specific lesion and subsequent psychometric test scores. This would agree with a recent report from a single institution registry of cognitive outcome, which reported that patients with simple shunt lesions who underwent complete repair had normal cognition when evaluated at school-age [16].

It is also worth drawing attention to the question of neurologic injury related to transcatheter procedures. Previous investigators have reported that gaseous microemboli are common during catheter placement of ASD occluder devices [17]. Krumsdorff and colleagues [18] reported thrombus formation around the ASD device was detected by transesophageal echocardiography in approximately 3% of patients following transcatheter ASD or patent foramen ovale closure. This would pose a risk for cerebral emboli. In spite of these potential risks for neurologic injury, long-term neurologic morbidity has not been reported [19].

The present study was designed to detect a four-point difference in psychometric test scores between the two patient groups with a power of 0.80. As such the present study does not exclude the possibility of very mild short-term cognitive deficits following non-complex open-heart surgery in children. In addition, the present study was limited to patients above 5 years of age in order to improve the validity of psychometric testing. It is possible that preschool children may be more prone to neurologic injury following exposure to CPB. Moreover, support techniques in more complex heart disease often involve more profound hypothermia. Care must be taken not to extrapolate the results from this study to other higher risk congenital heart patients. Several studies that have suggested that in newborns and infants undergoing congenital heart surgery longer duration of CPB is associated with neurologic

Table 4
Comparison of BRIEF™ assessment in surgery and transcatheter groups

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<th>Surgery</th>
<th>Transcatheter</th>
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<tr>
<td>Inhibit</td>
<td>104 ± 12</td>
<td>-2 ± 0</td>
</tr>
<tr>
<td>Shift</td>
<td>104 ± 12</td>
<td>-2 ± 2</td>
</tr>
<tr>
<td>Emotional control</td>
<td>101 ± 15</td>
<td>-3 ± 1</td>
</tr>
<tr>
<td>BRI index</td>
<td>100 ± 15</td>
<td>-1 ± 1</td>
</tr>
<tr>
<td>Initiate</td>
<td>102 ± 12</td>
<td>-5 ± 1</td>
</tr>
<tr>
<td>Working memory</td>
<td>99 ± 12</td>
<td>-3 ± 1</td>
</tr>
<tr>
<td>Plan/organization</td>
<td>100 ± 12</td>
<td>-3 ± 2</td>
</tr>
<tr>
<td>Monitor</td>
<td>98 ± 12</td>
<td>-2 ± 0</td>
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BRI, behavioral regulation index.
deficits. It is also possible that certain school-age children may be at higher risk than the cohort we have studied. Several investigators have shown that aortic and mitral valve replacement are more likely to produce post-operative neurologic injury than other closed heart procedures [20].

6. Conclusions

When compared to children undergoing transcatheter closure of surgical repair of lesions such as ASD, VSD and sub-aortic membrane does not result in detectable post-operative neurologic deficits. These data are important for counseling families and can contribute to the ongoing debate as to the relative merits of transcatheter versus surgical repair of certain heart lesions.

References