ORIGINAL ARTICLE

Neurodevelopmental outcome after cardiac surgery utilizing cardiopulmonary bypass in children

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ABSTRACT

Introduction: Modulating the stress response and perioperative factors can have a paramount impact on the neurodevelopmental outcome of infants who undergo cardiac surgery utilizing cardiopulmonary bypass. **Materials and Methods:** In this single center prospective follow-up study, we evaluated the impact of three different anesthetic techniques on the neurodevelopmental outcomes of 19 children who previously underwent congenital cardiac surgery within their 1st year of life. Cases were done from May 2011 to December 2013. Children were assessed using the Stanford-Binet Intelligence Scales (5th edition). Multiple regression analysis was used to test different parental and perioperative factors that could significantly predict the different neurodevelopmental outcomes in the entire cohort of patients. **Results:** When comparing the three groups regarding the major cognitive scores, a high-dose fentanyl (HDF) patients scored significantly higher than the low-dose fentanyl (LDF) + dexmedetomidine (DEX) (LDF + DEX) group in the quantitative reasoning scores (106 ± 22 vs. 82 ± 15 $P = 0.046$). The bispectral index (BIS) value at the end of surgery for the -LDF group was significantly higher than that in LDF + DEX group ($P = 0.011$). For the entire cohort, a strong correlation was seen between the standard verbal intelligence quotient (IQ) score and the baseline adrenocorticotropic hormone level, the interleukin-6 level at the end of surgery and the BIS value at the end of the procedure with an R^2 value of 0.67 and $P < 0.04$. There was an inverse correlation between the cardiac Intensive Care Unit length of stay and the full-scale IQ score ($R = 0.4675$ and P 0.027). **Conclusions:** Patients in the HDF group demonstrated overall higher neurodevelopmental scores, although it did not reach statistical significance except in fluid reasoning scores. Our results may point to a possible correlation between blunting the stress response and improvement of the neurodevelopmental outcome.

Key words: *Anesthesia and neurotoxicity, neurodevelopmental outcomes, pediatric cardiac surgery, role of anesthetics in modulating the stress response, stress response*

INTRODUCTION

Congenital heart defects are among the most common of all birth defects. It is estimated that more than 32,000 infants are born annually with congenital heart defects, representing one of every 125-150 children born in the United States. Advances in the care of children undergoing congenital cardiac surgery have greatly improved patient survival. Consequently, the largest population of patients with heart disease is now adults who are survivors of congenital cardiac disease, many with conditions that would have been considered incompatible with life only a few generations ago. As a result of this success, the best outcomes for children undergoing congenital cardiac surgery no longer focus on short-term survival, but rather the long-term neurodevelopmental achievement of these patients and their societal impact.[1-5] The purpose of this paper is to evaluate patients who have recently undergone congenital cardiac surgery to determine if there are any anesthetic or other perioperative variables that may have impacted their neurocognitive development.

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Neurodevelopmental outcomes are influenced by many factors[6] and include gender, the environmental impact of ethnicity and socioeconomic status, and also the underlying genetic predisposition. These outcomes may also be related to an insult *in utero* or they may be accentuated in the presence of cyanotic lesions in patients such as those with hypoplastic left heart syndrome.[4] The possible intraoperative impact of exposure to anesthetic agents, cardiopulmonary bypass (CPB), deep hypothermic circulatory arrest, hemodilution, hypoxemia, hypotension, and low cardiac output may also contribute to worsening the overall neurodevelopmental outcome.

The management of anesthetic agents and their impact on neonatal and infant cerebral neuronal development and apoptosis have recently received considerable attention.[7-11] Animal studies have reported conflicting results about the potential dangers of commonly used anesthetic agents. Investigators have implicated every available anesthetic agent including hypnotic agents like ketamine, induction agents such as propofol or sodium thiopental, barbiturates, narcotics, potent inhalational agents like isoflurane and even nitrous oxide. They have suggested that agents potentiating inhibitory transmission through gamma-amino butyric acid (GABA) receptors are problematic and also that medications decreasing excitatory transmission throughout N-methyl-D-aspartic acid (NMDA) glutamate receptors are dangerous. They have demonstrated that a vulnerable period of neurodevelopment exists for certain animal species exposed to extended anesthetics at very high doses, but none has been able to correlate these animal findings with outcome data in human subjects. There remains a significant knowledge gap as to the impact of anesthetic techniques as routinely titrated in pediatric patients and their associated long-term neurodevelopmental repercussions.

In a previous study, we evaluated the impact of narcotic dosing on the systemic stress response of children undergoing congenital cardiac surgery using CPB.[12] This study demonstrated that the use of a low-dose fentanyl (LDF) technique was inferior to a high dose fentanyl (HDF) technique or a LDF technique augmented with dexmedetomidine (DEX). Subjects in the LDF group had significantly higher inflammatory stress markers including adrenocorticotropic hormone (ACTH), cortisol, glucose, lactate, and epinephrine. These subjects also had a significantly higher cytokine ratio of interleukin-6 (IL)-6: IL-10 at 24 h postoperatively ($P < 0.0001$). Subjects in the LDF group had an increased postoperative opioid requirement ($P = 0.004$), longer prothrombin times ($P \leq 0.03$), and more postoperative chest tube output ($P < 0.05$). Given that the results of this study suggested a clear advantage to blunting the stress response utilizing a higher dose of fentanyl for these patients, we were interested in understanding if there were any long term developmental consequences of such an approach.

In this follow-up study, we evaluated the impact of the three different anesthetic techniques on the neurodevelopmental outcomes in the same cohort of patients from our previous study. As noted above, these children all underwent congenital cardiac surgery within their 1st year of life.

MATERIALS AND METHODS

The Institutional Review Board at Nationwide Children's Hospital approved this study, and written informed consent was obtained from a parent or guardian. The study was registered at http://www.clinicaltrials.gov (ID NCT00848393). Patients who previously underwent ventricular septal defect (VSD) closure, atrioventricular septal defect (AVSD) repair or tetralogy of Fallot (TOF) repair on CPB within their first 12 months of life, and who were previously included as a part of our stress response study comparing the use of LDF to HDF and LDF + DEX (LDF + DEX) were identified.[12] Of this cohort, patients who were ≤5 years of age were contacted by phone and enrolled in this study.

Children were evaluated by the Child Biobehavioral Outcomes Core at Nationwide Children's Hospital. Their intellectual functioning was assessed using the Stanford-Binet Intelligence Scales (5th edition) (SB-V). During the testing, parents were asked to rate their child's adaptive functioning using the Adaptive Behavior Assessment System (ABAS) and psychosocial adjustment using the Child Behavior Checklist (CBCL). Evaluations were completed blind to treatment group assignment.

Both patient clinical outcomes and neurodevelopmental outcomes were compared among the three study groups listed above. One-way AVONA or one-way layout nonparametric method, where appropriate, was used to test for effect differences among the three groups. A *post-hoc* test, Turkey pairwise comparison, was performed to detect a significant difference between pairs, when ANOVA test was significant. In addition, multiple regression analysis was used to determine the possible impact of the prenatal and perioperative factors on the neurodevelopmental scores. Furthermore, one sample *t*-test was used to compare the entire cohort of patients to the measurement mean of the general population. Type I error is strongly controlled at $\alpha = 0.05$ for single comparisons and with adjustment for multiple comparisons. The data were analyzed using the statistical software SAS version 9.2 (SAS Institute Inc., Cary, NC, United States).

We extensively examined maternal prenatal records, neonatal records, and all perioperative and postoperative data in an attempt to elicit any factors that impacted the developmental outcomes of these children. Prenatal factors included maternal and paternal highest level of education attainment, employment, and ethnicity. Other prenatal factors included the history of maternal drug use during pregnancy, method of delivery (vaginal vs. cesarean section), birth weight, and gestational age at the time of delivery and birth order of the child.

Perioperative factors included age and weight at the time of the surgery, gender, and anesthetic agents used. In addition, perioperative hormonal and cytokine response measurements were reviewed. Hormonal stress markers included ACTH, cortisol, adrenaline (epinephrine), and noradrenaline (norepinephrine). Measured cytokines included IL-6, IL-8, IL-10, and tumor necrosis factor-α. Perioperative blood usage was analyzed along with the length of stay in both the cardiac Intensive Care Unit (CTICU) and the total hospital length of stay.

Outcomes measured on the SB-V included fluid reasoning, working memory, quantitative reasoning, knowledge, visual-spatial processing, nonverbal intelligence quotient (IQ), verbal IQ, and full-scale IQ. The scores are all standardized (mean = 100, standard deviation [SD] = 15). The ABAS-II provides a General Adaptive Composite, as well as standard scores for conceptual, social, and practical composite domains. All scores on the ABAS are standardized (mean = 100, SD = 15).

The conjoint behavioral consultation (CBC) provided a total problems standard score, as well as standard scores for internalizing and externalizing problems (mean = 50, SD = 10). We also examined subscales (i.e., emotionally reactive, anxious/depressed, somatic complaints, withdrawn, sleep problems, attention problems, aggressive behavior), as well as Diagnostic and statistical manual of mental (DSM) disorder scales (affective problems, anxiety problems, pervasive developmental problems, attention deficit/hyperactivity problems, oppositional defiant problems). All scores were standardized (mean = 50, SD = 10).

RESULTS

A total of 49 patients were included in the original stress response study. Six patients underwent their surgical repair after 1-year of age and were excluded from the evaluation process of the current study. Two patients were deceased. Eleven families refused to participate in the study. Nine patients could not be reached due to relocation to other states or outside the country leaving a total of 21 patients for the current study. There were nine patients from the LDF group, five patients from the HDF group, and seven patients from the LDF + DEX group. Patients in the LDF + DEX group included patients with trisomy 21. Given that the focus of the study was neurocognitive outcome, their data were excluded. Therefore, the final cohort included 19 patients.

There were no significant demographic differences other than gender [Table 1]. Patients in HDF group included more female subjects than those in the LDF + DEX group ($P = 0.01$). There were no significant differences between the three groups regarding the type of the cardiac lesion. When comparing the minimum alveolar concentration (MAC)-hour of inhalational agent use among the three groups, there was no difference between the groups [Figure 1].

The bispectral index (BIS) value at the end of surgery for the LDF group was significantly higher than that in LDF + DEX group (58 ± 9 vs. 42 ± 12, $P = 0.011$). In addition, baseline lactate for the LDF group was lower than that in LDF + DEX group (0.6 ± 0.1 vs. 1 ± 0.3, $P = 0.0153$). Poststernotomy glucose for the LDF group was higher than HDF (125 ± 23 vs. 89 ± 16, $P = 0.048$).

Table 1: Demographics and perioperative data

Variables	LDF	LDF + DEX	HDF
Birth weight (kg)	3.1±0.6	3±0.5	3.1±0.6
Age at time of surgery (months)	5±2	4±1	4±1
Weight at time of surgery (kg)	6.1±0.94	5±1	6.2±1.4
Length of CTICU stay (days)	1.75±1	3.5±5	1.2±0.4
Length of hospital stay (days)	4.75±1.5	6.2±5.8	4.2±1.2
Gender	7 male/2 female	6 male/0 female	1 male/4 female**
CPB time (min)	127±21	123±56	109±29
Aortic cross clamp time (min)	87±25	89±46	73±23
Age at time of evaluation (months)	36±8	34±7	39±7

LDF: Low-dose fentanyl, DEX: Dexmedetomidine, HDF: High-dose fentanyl, CTICU: Cardiac Intensive Care Unit, CPB: Cardiopulmonary bypass. **$P=0.01$ compared to the LDF + DEX

When comparing the three groups regarding the major cognitive scores, the HDF patients scored significantly higher than the LDF + DEX group only in quantitative reasoning (106 ± 22 vs. 82 ± 15 $P = 0.046$) [Table 2]. There were no other significant differences between the three groups; however, patients in the LDF + DEX had the lowest IQ scores among the three groups. This trend did not continue in the ABAS-II and CBCL scores [Table 2]. When comparing the entire cohort of patients to the general population, our patients had significantly lower working memory (91 ± 13 vs. 100 ± 15, $P = 0.008$), verbal IQ (88 ± 18 vs. 100 ± 15, $P = 0.016$), and full-scale IQ (91 ± 16 vs. 100 ± 15, $P = 0.03$) scores. Our patients' adaptive (ABAS-II) and behavioral (CBC) scores were not significantly different from standardized control values [Table 2].

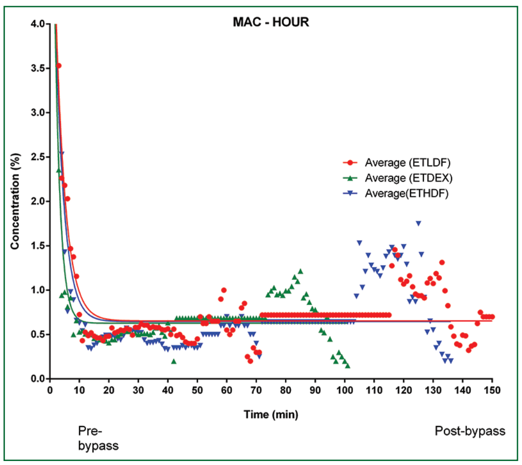

Figure 1: Minimum alveolar concentration-hour

Multiple regression analysis demonstrated some correlation, in some cases very strong, between different perinatal, parental, and perioperative factors and neurodevelopmental outcomes. A positive correlation was evidenced between the DSM-attention deficit hyperactivity scores and the ACTH level at baseline, CPB time, epinephrine level on CPB, and steroid use ($R^2 = 0.778$ and $P < 0.005$). Another positive correlation was seen between the verbal IQ score and the baseline ACTH level, the IL-6 level at the end of surgery and the BIS value at the end of the procedure ($R^2 = 0.67$ and $P < 0.04$). There was a negative correlation between the CTICU length of stay and the full-scale IQ score ($R^2 = -0.467$ and $P = 0.027$). There was a positive correlation between BIS value at the end of surgery and the verbal IQ standard score ($R^2 = 0.67$ and $P = 0.007$). There was another positive correlation between the use of steroids and the DSM-attention deficit/hyperactivity T-score ($R^2 = 0.77$ and $P = 0.005$) [Table 3].

When looking at the impact of the parental and perinatal factors on the neurodevelopmental scores, the patient's ethnicity had some correlation with the CBCL sleep problems score. Patients of white/Caucasian ethnicity had a lower sleep problem T-score ($R^2 = 0.56$ and $P = 0.043$). Ethnicity had a correlation with the ABAS-functional preacademic scaled score, where white/Caucasians had a lower score, compared to nonwhite ($R^2 = 0.44$ and $P = 0.006$).

Table 2: Comparing major cognitive, adaptive, and behavioral outcomes between the three groups and the entire cohort of patients to the general population

Scores	LDF	LDF + DEX	HDF	All patients	Control	*P* value (all patients vs. control)
Quantitative reasoning score	96±18	82±15	106±22	95±20	100±15	0.34
Knowledge score	97±10	95±12	91±27	95±16	100±15	0.19
Visual spatial processing score	97±16	92±7	91±17	94±14	100±15	0.12
Working memory score	92±10	84±13	94±17	91±13	100±15	0.008
Nonverbal IQ score	98±15	89±6	92±19	94±14	100±15	0.12
Verbal IQ score	91±17	80±8	93±26	88±18	100±15	0.016
Full-scale IQ score	94±15	83±5	93±24	91±16	100±15	0.03
ABAS-II motor scaled score	10±3	11±3	8±3	10±14	10±3	0.85
ABAS-II general adaptive scaled score	102±13	100±13	96±21	100±16	100±15	0.91
ABAS-II conceptual adaptive domain composite score	106±16	99±13	99±21	102±24	100±15	0.46
ABAS-II social adaptive domain composite score	106±8	105±13	102±24	99±13	100±15	0.95
ABAS-II practical adaptive domain composite score	96±14	95±11	93±15	95±2	100±15	0.14
CBC internalizing problems score	44±8	49±4	44±13	45±9	50±10	0.049
CBC externalizing problems score	45±10	51±10	45±11	46±10	50±10	0.19
CBC total problems score	43±8	50±9	44±12	45±9	50±10	0.055

LDF: Low-dose fentanyl; DEX: Dexmedetomidine; HDF: High-dose fentanyl; CTICU: Cardiac Intensive Care Unit, IQ: Intelligence quotient; ABAS: Adaptive Behavior Assessment System; CBC: Conjoint behavioral consultation

Table 3: Correlation between perioperative variables and neurodevelopmental scores

Neurodevelopmental score	Correlating perioperative variables	R^2	*P* value
DSM-attention deficit hyperactivity scores	ACTH level at baseline, CPB time, epinephrine level on CPB and steroid use	0.778	<0.005
Verbal IQ score	Baseline ACTH level, IL-6 level at the end of surgery and BIS value at the end of the procedure	0.67	<0.04
Full-scale IQ score	CTICU length of stay (inverse correlation)	0.4675	0.027
Verbal IQ score	BIS value at the end of surgery	0.67	0.007

DSM: Diagnostic and statistical manual of mental disorders; IQ: Intelligence quotient; ACTH: Adrenocorticotropic hormone; CPB: Cardiopulmonary bypass; IL: Interleukin; BIS: Bispectral index; CTICU: Cardiac Intensive Care Unit

DISCUSSION

While our data may have failed to demonstrate a strong difference between the three groups based on blunting of the stress response and the improvement of the neurodevelopmental outcomes, there was some significant improvement of the fluid reasoning scores in patients who received HDF when compared to LDF + DEX. Patients in the HDF group demonstrated overall higher neurodevelopmental scores, although it did not reach statistical significance. This could be due to the low number of patients who were recruited in this portion of the study, although many studies have failed to demonstrate a correlation between blunting of the stress response in children undergoing cardiac surgery utilizing CPB and improved outcomes.[13-17]

While previous animal studies have demonstrated the possible neuroprotective effect of DEX,[18] our results show no difference and in some instances, worsening of the neurodevelopmental scores in the LDF + DEX group of patients. Again, this could be due to the small cohort of patients available to the study; our results here failed to replicate a difference in the stress response between the LDF and LDF + DEX group which was reported in our original study.[12]

When looking at the entire cohort of patients, there was a notable positive correlation between both verbal IQ scores and functional preacademic scores and the following stress response markers: ACTH, epinephrine, IL-6, and cortisol level. The suggestion that reducing surgical inflammatory markers through anesthetic exposure leads to improved neurodevelopmental outcomes is very interesting. This association was strongly noted even in the presence of a small patient sample size. It is conceivable that a larger population would further support the advantages of an anesthetic that provided a deeper plane of anesthesia and effective blunting of the inflammatory stress response.

Our finding corroborate previous research in both adults and children that have looked at the deleterious impact of perioperative factors such as CPB time, BIS level, and CTICU length of stay. Our recorded BIS values positively correlated with verbal IQ scores. This could be interpreted as patients with lower BIS values had lower verbal IQ scores. Adult studies have demonstrated the correlation of BIS scores below 45 and postoperative mortality.[19] However, the caveat in our results is the differences in electroencephalography (EEG) patterns from neonates and infants versus adults which may impact the application of the BIS in this population. It is also possible that preexisting conditions resulted in alterations of the EEG thereby result in a lower BIS number given a similar depth of anesthesia. Other studies have linked low and isoelectric BIS scores with delayed awakenings and documented intra-procedural cerebral ischemic infarctions.[20]

Length of CTICU stay negatively correlated with the full-scale IQ. These results are in agreement with a recent study on the neurodevelopmental outcomes in children with congenital heart diseases, where Marino *et al*.[21] demonstrated that prolonged hospital stay and CTICU stay were associated with poorer late cognitive function and that patients in the longest quartile of CTICU length of stay had an average IQ that was 7.2 points lower than those patients in the shortest quartile.

Our cohort of patients scored significantly lower in working memory, verbal, and full-scale IQ scores in comparison to the general population. These results are in line with other studies that have documented that children who have undergone surgical correction of CHD demonstrate a wide variety of neurodevelopmental delays including speech delay, cognitive impairment, delayed visual-spatial and visual-motor skills, attention deficit disorder, and other associated motor delays and learning disabilities.[22,23] It is worth mentioning that the adaptive and behavioral outcomes for our patients were not different from the general population.

The limitations of this study include the previously mentioned small sample size. It is also a limitation that this study was conceived after completion of the initial stress response study and thus, eliminated the possibility of obtaining presurgical baseline neurodevelopmental evaluations. It is also unfortunate that 11 families declined to participate and that 9 families were unreachable because of relocation. It is worth noting that there were no differences between the three groups based on parental and perinatal variables, which speaks to good randomization of the three groups.

Exposure to anesthetic agents adds another variable in the consideration of what contributes to the most successful long-term outcome after pediatric cardiac surgery. Anesthetic agents have proven to be neurotoxic to animals at high-doses over extended periods of time; it is unclear how this applies to human subjects exposed to a standard anesthetic. Our results are noteworthy in that they suggest the importance of administering a depth of the anesthetic that not only renders them amnestic, but one that also minimizes the systemic inflammatory stress response. This is a cautionary note worth considering. In our current quest to do no harm via exposure to anesthetic agents, it is worth remembering that failure to adequately anesthetize patients may also incur a long-term neurodevelopmental risk.

When considering the population of patients with congenital heart disease, it is axiomatic that some of them will have a cerebral insult or anomaly prior to surgery, some of them will have existing chromosomal abnormalities, and some will live with cyanosis of varying severity.[24,25] They all will live within family systems that are tremendously stressed by the gravity of the disease. But as we work to lead each patient to their best possible outcome it is imperative that we continually try and refine our approach to treatment modalities and anesthetic care specifically with the goal of long-term developmental success at the forefront of our awareness. The question is no longer if these patients will survive, but rather, what we can do to help them thrive.

In our endeavor to achieve this goal of the best possible neurodevelopmental outcome for this group of patients, our next step is to perform a study with the aim of evaluating children undergoing cardiac surgery under year of age at baseline and then at 1 month, 3 months, 6 months, and 1 year postoperatively. In addition, we will try to study the impact of blunting the stress response on the levels of two of the cerebral injury biomarkers (serum S-100β and neuron-specific enolase) and their correlation with these neurodevelopmental outcomes. We will follow these children until school age.

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