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Feasibility and Pilot Study of the Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) Project

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Role: All of the PANDA Research Network Co-investigators participated in the design of the study.

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Abstract

Background—Animal studies have documented that exposure of the developing brain to commonly used anesthetic agents induce neurotoxicity and late abnormal neurobehavioral functions as adults. Results from clinical studies have all been performed using existing datasets, and produced inconsistent results. To provide more definitive evidence to address the clinical relevance of anesthetic neurotoxicity in children, an interdisciplinary team of investigators designed and developed the Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) project. We present pilot study results in 28 sibling pairs recruited and tested at Columbia University Medical Center (CUMC) and Children's Hospital of Boston (CHB) for the PANDA project.

Methods—The PANDA project uses an ambi-directional cohort design. We performed prospective neuropsychological assessment in 28 exposed-unexposed sibling pairs ages 6–11 years old. The exposed siblings were ASA 1 or 2 and had received a single episode of anesthesia for inguinal hernia repair prior to age 36 months and the unexposed siblings had no anesthesia before age 36 months. All sibling pairs were English speaking and were 36 weeks gestational age or greater. Each sibling pair underwent direct testing using WASI and NEPSY II, and the parents completed questionnaires related to behavior using CBCL and Conners' rating. Data are presented as means $\pm$ SD. We conducted descriptive analyses of demographic data. We compared exposed and unexposed sibling groups on WASI and NEPSY II, and total and T-scores from CBCL and Conners' as continuous data by paired t test between. A $P < 0.05$ was considered significant.

Results—Following IRB approval for the study at both CUMC and CHB, the full PANDA study protocol was implemented to perform a pilot feasibility study. Our success rate was 96.7% in obtaining detailed medical and anesthesia records in our historical cohort. Scores for verbal IQ (Exposed=106.1 $\pm$ 16.3, Unexposed=109.2 $\pm$ 17.9), performance IQ (Exposed=109.1 $\pm$ 16.0, Unexposed=113.9 $\pm$ 15.9) and full IQ (Exposed=108.2 $\pm$ 14.0, Unexposed=112.8 $\pm$ 16.8) were comparable between siblings. There were no differences between the two groups in T scores for any of the NEPSY II sub-domains, CBCL or Conners'. An abstraction protocol with web-based electronic data capture forms also was developed in conjunction with the International Center for Health Outcomes and Innovation Research (InCHOIR).

Conclusions—The pilot study provided useful information for feasibility to recruit the sample size and to obtain relevant clinical data. For the final study protocol, both the neuropsychological battery and the age range for testing were revised. Our results confirmed the feasibility of our study approach, and yielded pilot data from neuropsychological testing.

Keywords

Children; Anesthetic neurotoxicity; Neurodevelopment; Outcome

Introduction

Children, unlike adults, frequently receive general anesthesia for not only surgical procedures, but also for dental and diagnostic imaging procedures including magnetic resonance imaging, positron emission tomography and computerized tomography. It has been estimated that 6 million (or 10%) of American children (including 1.5 million infants)

undergo anesthesia annually for surgical¹ or non-surgical procedures. The large numbers of children who are exposed to anesthetic agents thus make the long-term safety of anesthesia a significant public health issue.

The Food and Drug Administration (FDA)'s Anesthetic and Life Support Drugs Advisory Committee² met in 2007 to discuss the safety of anesthetic agents in children, principally in response to findings from pre-clinical studies demonstrating anesthetic neurotoxicity in the developing brain.³⁻³¹ Since that time, several clinical and epidemiological studies have been published that specifically examined the association of anesthesia and neurodevelopment.³²⁻³⁹ However, results of currently available clinical and epidemiological studies remain inconclusive to guide clinical decision-making.^{40,41} All of the studies, to date, have significant limitations. Among them are: (1) retrospective study design and inadequate control for known and unknown confounders; (2) lack of detailed information about anesthetics such as specific type of the agent, dose and duration; (3) exposure to outdated anesthetic agents (e.g., halothane was the agent used in the Olmstead County studies,^{32,33,39} and is no longer in use today); and (4) varied outcome measures, including learning disability, diagnosis of developmental delay, academic performance and parental reports of behavior. These limitations may have contributed to the inconsistent findings from currently published clinical studies. To better inform anesthesia practice and provide more definitive clinical evidence to address this research gap, an interdisciplinary team of investigators proposed and designed the multi-site Pediatric Anesthesia NeuroDevelopment Assessment (PANDA) study.

The PANDA project uses an ambi-directional cohort design. It proposes to perform prospective assessment of neuropsychological functions in a retrospective cohort of children. The exposed cohort consists of children who had anesthesia for inguinal hernia repair before age 36 months and the unexposed cohort are their siblings without any anesthesia exposure prior to age 36 months. The research design and rationale of the PANDA project are described in detail elsewhere.⁴² In this article, we present pilot study results from 28 sibling pairs recruited and tested at Columbia University Medical Center (CUMC) and Children's Hospital of Boston (CHB), as well as the process of designing the PANDA study, which was informed by scientific symposia and a neuropsychologist workshop. Our results document the feasibility of an ambi-directional study approach that combines the collection of relevant historical clinical information related to anesthesia exposure with prospective assessment of neuropsychological and behavioral outcome.

Methods

During the planning phase of the PANDA study, we collected data from all PANDA study sites to survey anesthesia practice and document recruitment feasibility. We submitted and successfully obtained IRB approval at all PANDA network study sites, and written informed consent was obtained from parents or legal guardians and assent was obtained from the study subjects when indicated.

To estimate the likely yield of eligible and recruitable study subjects, we surveyed the total inguinal hernia surgical volume at all study sites, and projected the yield using the analysis we performed at CUMC.

We implemented the full study protocol including reviewing medical and anesthesia records, abstracting data of clinical history and anesthesia exposure, and performing direct neuropsychological assessment and obtaining detailed information on behavior from parental questionnaires in a total of 56 subjects (28 sibling pairs) at CUMC and CHB. Specifically, at CHB and CUMC, we reviewed anesthesia billing records and identified

ASA physical status 1 (totally healthy) and ASA physical status 2 (essentially healthy with minor health issues that have no effect on functions of daily living) children who had inguinal hernia repair between 2000 and 2006. We then further reviewed their available medical records to confirm that they fulfilled inclusion criteria and did not meet any of the exclusion criteria. At CHB, they were then contacted by mail to determine whether they would agree to further discuss the study by phone. At CUMC and CHB, the families of the potential study subjects were then contacted by phone to ascertain eligibility using an IRB-approved phone script. Those eligible study subjects who consented to participate in the study were then scheduled for testing.

We conducted direct neuropsychological testing using the Wechsler Abbreviated Scale of Intelligence (WASI) to assess global cognitive function and NEuroPSYchological Assessment, second edition (NEPSY II) to assess domain-specific cognitive functions. To assess behavioral functions, we administered parental questionnaires using the Child Behavior Checklist, age 6–18 years (CBCL 6–18) and Conners' Parent Rating Scales (3rd Edition). WASI and NEPSY II were performed simultaneously by trained personnel in both siblings at CUMC and sequentially at CHB. A pediatric neurodevelopmental specialist at CUMC (MB) and a neuropsychologist at CHB (DB) performed scoring. Medical and anesthesia records were reviewed by pediatric anesthesiologists (CI and TM) to abstract clinical information and anesthesia exposure data using the Case Report Form that had been specifically developed for the PANDA study. Data abstraction was then separately performed by the PI (LS) to validate reliability and confirm consistency.

We conducted descriptive analyses of demographic data and compared exposed and unexposed sibling on outcome measures in global cognitive function, domain-specific cognitive functions and behavioral functions. Demographic data are presented as means $\pm$ SD. Testing scores in WASI and NEPSY II, and total and T-scores from CBCL and Conners', were analyzed as continuous data by paired t-test between exposed and non-exposed sibling groups. We also compared between the two sibling groups the percentage of children whose CBCL scores or Conners' scores were considered "atypical".

Results

I. Collecting Quantitative Data in Pilot Feasibility Study

Pilot feasibility study was performed at CUMC and CHB. A total of 52 children (26 sibling pairs) and 6 children (3 sibling pairs) were identified and scheduled at CUMC and CHB, respectively. Fifty-six children (28 sibling pairs) successfully completed and yielded test results that were scored. Parents expressed unsolicited satisfaction with the testing process and children participated enthusiastically even at the end of the school day.

Detailed demographics are presented in Table 1. The exposed subjects in our pilot study were predominantly male (n=26), white (n=24), and ASA 1 (n=24).

Clinical Information and Anesthesia Exposure (Table 2)—We were able to obtain and review the paper medical records in all except one child who had anesthesia and surgery in 2002 at CUMC. We completed data abstraction from anesthesia records in 27 out of 28 study subjects.

Twenty-six children received inhaled volatile general anesthesia for inguinal hernia surgery, and one child received a spinal anesthetic as the sole agent with no additional drugs. In all except one case an inhaled volatile agent was co-administered with nitrous oxide. Three children received premedication with midazolam and 7 children received supplementation with propofol. Twenty children received a combination of at least two or more inhaled

volatile agents or a combination of an inhaled volatile agent with propofol or midazolam. Duration of anesthesia ranged from 25 to 225 minutes in the 26 patients who had general anesthesia and averaged 99 minutes (SD=47 minutes). It was less than 120 minutes in 19 cases, with close to half lasting between 60 to 120 minutes (n=12). There were no recorded abnormal vital signs or oxygen saturation, or intraoperative adverse events.

Neuropsychological and Behavioral Assessment Results (Table 3)—To assess global cognitive function, we used WASI to obtain verbal, performance, and full IQ scores. All average IQ scores were above the population mean (100) for both exposed and unexposed siblings. There were no differences in average scores between the two groups.

We used the full NEPSY II battery to assess all of the sub-domains of neurocognitive functions. Age range boundaries for some of the subtests precluded both siblings in some pairs from being tested on some subtests. In our final PANDA battery, we have retained a subset of NEPSY II to allow study subjects to be within the age range appropriate for all of the proposed tests. Results of those subtests in the final battery are shown (Table 3).

Total and T-scores for CBCL for externalizing, internalizing and DSM-oriented behaviors, obtained from parental reports, were comparable between the exposed and unexposed groups and were all within normal limits. There were no differences with respect to the proportion of “atypical” scores between the exposed and unexposed groups. No differences in Conners’ rating scales were found between the two groups (data not shown).

II. Addressing Methodological Issues in Planning of PANDA Study

Scientific Symposia and Neuropsychological Workshop—Scientific symposia were held in 2008 and 2010 to define the PANDA research question, and develop and refine the study design. They informed our study design using an ambi-directional approach that collects prospective and direct neuropsychological data on the effects of a single episode of anesthesia exposure on long-term neurocognitive function and behavior in healthy children. The choice of unexposed sibling as the comparison group aims to minimize many major known confounders: parental education, family environment, and socioeconomic class. The age of exposure of 0–36 months was based on existing data on peak synaptogenesis in the developing human brain. Our proposed age of assessment was 6–11 years of age so that we could determine the long-term outcome of early childhood exposure with sufficient time interval between exposure and assessment. The age of assessment was later revised with the finalized neuropsychological testing battery. We specifically convened a two-day neuropsychological workshop in June 2010 with participation of all neuropsychological co-investigators. The workshop produced a complete neuropsychological battery that could be completed in two hours (Table 4). The battery permits evaluation of global and domain-specific neurocognitive functions as well as behavior. All of these neurocognitive outcomes have been demonstrated to be critical for school performance and daily living. The neuropsychology co-investigators also discussed the importance of testing executive function and administering the same, age-appropriate tests to all children. The age of assessment was thus revised upwards to 8–15 years.

CUMC Recruitment and Projections of Available Study Subjects (Fig. 1)—We used billing records and medical records at CUMC to perform the initial screening. Details are presented in Figure 1.

The analysis we performed at CUMC was then used to project the available study subjects from all study sites. A comparable yield of 8.2% in a total of more than 20,000 inguinal hernia surgical procedures in ASA 1 and ASA 2 children under 36 months of age from all

participating study sites would produce 1,640 eligible study subjects and 960 subjects available to participate. This is approximately twice the required sample size for the study.

Developing the Case Report Form to Abstract Clinical Information and Anesthesia Exposure—We developed and then field-tested a Case Report Form for our study, which includes (1) detailed medical history from birth until the time of testing, including any school history related to learning disability or need for individualized educational programs; (2) family history including family composition, changes in family composition, a group of questions specifically related to the family's socioeconomic status; and (3) anesthesia exposure information. Data related to medical history and family history were obtained through review of medical records and direct interviews with parents at the time of the study visit. Anesthesia exposure information is obtained through review of anesthesia records and initially reviewed by a pediatric anesthesiologist and then cross-checked by a second pediatric anesthesiologist. Specifically, anesthesia exposure information includes anesthetic agents used, duration of use of inhaled anesthetics, total dose of all drugs used, any noted unanticipated changes in vital signs, and documented intraoperative adverse events.

Detailed abstraction protocol for anesthesia data was developed and pilot tested in 10 cases at each of the study sites. We worked closely with the International Center for Health Outcomes and Innovation Research (InCHOIR) to convert the Case Report Form for web-based electronic data capture.

Conclusions

Our results establish that it is feasible to use an ambi-directional cohort approach to evaluate neurocognitive outcome following early childhood anesthesia exposure. Our pilot data addressed two major challenges for using an ambi-directional cohort design for the PANDA study: (1) recruitment from a historical cohort of children who had inguinal hernia surgery before age 3 years and (2) obtaining reliable clinical data related to anesthesia exposure and surgery up to 10 years later. We successfully completed our proposed initial study protocol in 56 children (28 sibling pairs), and made refinements and revisions to finalize the PANDA study protocol.

We chose children undergoing inguinal hernia surgery as the exposure group because inguinal hernia surgery is a common outpatient pediatric surgical procedure and there is no known association between inguinal hernia and neurodevelopmental conditions. Because we have no scientific data to specify the “phenotype” for the neurodevelopmental outcome following early childhood anesthetic exposure, we considered birth to 3 years of age to be the potentially vulnerable period, since it spans the period for peak synaptogenesis in different regions of the human brain.⁴³⁻⁴⁷

As a pilot feasibility study, our research team was able to recruit participants and successfully complete the study protocol in more than half of all potential study subjects who were deemed eligible, with 50% of all eligible study subjects agreeing to participate in our study. These results might introduce participation bias, with self-selection of those families with healthier children. However, with the expressed purpose of our study, it would be equally likely for families with concerns about their child's development to self-select to participate. We had one child with special needs that was unable to complete the testing. The average interval was seven years between exposure and testing in our exposed sibling. Thus it is possible to recruit from a historical pediatric cohort using medical records even when these children are no longer current patients at the study site.

We have identified several areas for improvement to enhance recruitment of study subjects and are working to establish “best practices” that would encourage and support parents to participate in our study.

In the pilot feasibility study, our success rate was 96.7 % to obtain all medical records in our historical cohort. With six of seven PANDA study sites now using electronic anesthesia records (UMCH, VCH, CHOP, CUMC, CCHMC, and CHP), and several with electronic anesthesia records for the entire period from 2000 to 2010, we project our overall success rate to obtain medical records to be the same or better with the full PANDA project. We further demonstrated the effective use of the standardized PANDA-specific data abstraction protocol to reliably and consistently record data of anesthetic agents used, duration of inhaled agent exposure, and total doses of intravenous drugs.

At both CUMC and CHB, we confirmed that the prospective assessment arm of the ambi-directional cohort study protocol could be successfully completed. Only one scheduled study subject, a child who was enrolled in a special education program, could not complete the test battery. Our experience in this study subject has led to the development of guidelines in scheduling and testing when a child has special needs or may be ill.

Based on our experience with testing, we found child interactive assessments and parent reports effective and feasible. We could administer a comprehensive neuropsychological battery within two hours that specifically assessed global IQ (WASI), verbal fluency, speeded naming, receptive language and visual memory (subtests within NEPSY II), and behavior (CBCL and Conners).

Our results guided the revision of study protocol including revision of our initial test battery to add more detailed examination of executive function, a neurocognitive function subserved by the prefrontal cortex that continues to develop into adolescence. We have thus revised the age range for testing to 8–15 years. We also established training and test administration criteria for testers and the training protocol for test administration.

Our results also provided insight into patient demographic characteristics in the proposed target population in the PANDA study. Inguinal hernia surgical patients are known to be predominantly male and this was confirmed in our pilot study. At the same time, the results of the ASA status among 28 inguinal hernia patients (24 were classified as ASA I and the remaining four ASA 2 patients had no serious medical conditions or received any medications) suggest that future results from PANDA study could be generalizable to the healthy, elective pediatric surgical population, although gender needed to be included in data analysis.

In conclusion, we tested the applicability and feasibility of an ambi-directional cohort design to address the critical public health and child health issue related to the neurodevelopmental effects of early childhood exposure. The PANDA study will leverage the advantages of such an approach to produce outcome data efficiently. The PANDA study will also use a sibling comparison group to minimize the contribution of confounding from genetic influences, socioeconomic status, and parental education. Our pilot study results have demonstrated the feasibility of an ambi-directional cohort approach to implement the PANDA study. We showed that we could identify and recruit the needed sample size of eligible study subjects, reliably and consistently abstract clinical information and anesthesia exposure data in a historical cohort, administer the neuropsychological battery to directly assess global and domain specific neurocognitive functions, and obtain information related to behavior using standardized, validated parental questionnaires.

We fully recognize that results from the PANDA study will only start to address the important issue of anesthetic effects on neurodevelopment in children. Since the great majority of US children exposed to anesthesia are healthy children undergoing elective procedures, our study would have an important impact from the public health perspective. If we find significant neurocognitive effects, then changes in current pediatric anesthesia/surgical care will need to be considered. This will require the active engagement of clinicians, parents, and governmental agencies. Important topics in the discussion of risks and benefits will include which elective procedures could be delayed, what are the risks for delay, what are the possible alternative approaches in terms of anesthetic techniques and agents, and what are possible mitigating or protective strategies that could be deployed. If we find no anesthesia effects, then we could offer reassurance to millions of parents.

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Figure 1.**Recruitment Flowchart**

We used billing records and medical records at CUMC to perform the initial screening. Of the 394 who passed the initial screening, we were able to successfully make phone contact in 207 subjects. 26 of the total 45 subjects who were deemed eligible underwent testing.

Table 1

Demographic Characteristics

A. General Demographics		
	Exposed	Unexposed
Age (months)	101.1 ±17.6	109±23.9
Age of anesthesia exposure (months)	16.4±11.5	NA
Gender		
Male	26	12
Female	2	16
ASA status		
ASA 1	24	NA
ASA 2	4	NA
Race/ethnicity		
White	23	23
Hispanic	2	2
Black	2	2
Other	1	1

B. Sex Concordance of Sibling Pairs	
Exposed-Unexposed	n
Male-Male	10
Male-Female	16
Female-Male	2
Female-Female	0

C. Birth Order in Sibling Pairs		
	Exposed-Unexposed (n)	Age Difference (months)
Birth Order		
Younger-Older	16	-30.7±8.3
Older-Younger	9	+30.0±8.1
Twins	3	
Overall		+27.2±12.2

D. Age at Testing and Age of Anesthesia Exposure		
	Age at Testing (months)	Δ Time (Exposure & Testing) (months)
Overall	101.1±17.6	84.8±17.6
Exposure at age 0-12 months (n=7)	95.1±17.6	91.3±15.5
Exposure at age 13-24 months (n=10)	102.7± 17.7	85.7±18.7
Exposure at age 25-36 months (n=8)	106.6±17.2	75.4±16.5

Table 2**Anesthetic Exposure During Inguinal Hernia Surgery**

A. Types and Duration of Inhaled Anesthetic Agents		
	n	Duration of exposure (min±SD)
Sevoflurane	24	22.0±20.2 (5-60)
Isoflurane	13	50.2±19.9 (20-95)
Halothane	5	42.0±37 (10-100)
Nitrous Oxide	25	50.3±28.6 (5-120)

B. Duration of Anesthesia	
	n
0-60 minutes	7
61-120 minutes	12
> 120 minutes	7

Table 3

Results of Neurocognitive and Behavioral Assessment

1. IQ Scores from WASI			
	Verbal IQ (mean $\pm$SD)	Performance IQ (mean $\pm$SD)	Full IQ (mean $\pm$SD)
Exposed (n=28)	106.1 $\pm$ 16.3	109.1 $\pm$ 16.0	108.2 $\pm$ 14.0
Unexposed (n=28)	109.2 $\pm$ 17.9	113.9 $\pm$ 15.9	112.8 $\pm$ 16.8

2. NEPSY II		
	Exposed (n=28)	Unexposed (n=28)
NEPSY II		
Comprehension of Instructions	12.0 $\pm$ 1.9	12.0 $\pm$ 3.3
Memory of Faces	11.7 $\pm$ 3.6	10.7 $\pm$ 3.4
Delayed Memory of Faces	11.3 $\pm$ 3.5	10.5 $\pm$ 3.2
	Exposed (n=23)	Unexposed (n=24)
Speeded Naming	8.2 $\pm$ 5.3	10.7 $\pm$ 4.1
	Exposed (n=20)	Unexposed (n=21)
Visuomotor Precision	10.1 $\pm$ 2.5	10.0 $\pm$ 3.5

3. Child Behavior Checklist (CBCL)		
	Exposed (n=28)	Unexposed (n=28)
T Score (mean $\pm$SD)		
Internalizing	46.7 $\pm$ 8.8	48.1 $\pm$ 10.9
Externalizing	47.8 $\pm$ 8.4	48.0 $\pm$ 9.3
Total Problems	47.6 $\pm$ 7.8	46.5 $\pm$ 9.8
T Score (DSM Oriented) (mean $\pm$SD)		
Affective	52.4 $\pm$ 4.3	53.9 $\pm$ 4.8
Anxiety	51.3 $\pm$ 2.7	54.2 $\pm$ 6.6
Somatic	54.0 $\pm$ 5.1	52.4 $\pm$ 4.4
ADHD	53.0 $\pm$ 4.5	52.3 $\pm$ 4.0
Opposition Defiant	54.1 $\pm$ 5.1	54.3 $\pm$ 4.5
Conduct	53.1 $\pm$ 4.8	52.8 $\pm$ 4.6

Table 4**PANDA Study Neuropsychological Testing Battery**

Neurocognitive Outcomes (Subdomain/Subprocess)	Domains	Assessment Instruments
1. Global cognitive function (IQ)	Global Cognitive Function	1. WASI
2. Visual memory 3. Verbal memory	Memory/Learning	2. Faces, Delayed Faces (NEPSY II) 3. CVLT-C
4. Motor speed & dexterity 5. Processing speed	Motor/Processing Speed	4. Grooved Pegboard 5. Coding (WISC-IV)
6. Visuospatial function	Visuospatial	6. Block Design, Matrix Reasoning (WASI)
7. EF components 8. Working memory 9. Sustained and selective attention, impulsivity 10. Cognitive flexibility 11. Verbal fluency	Attention/ Executive Function	7. BRIEF 8. Digit Span (WISC-IV) 9. CPT II 10. DKEFS Trails Making 11. Word Generation (NEPSY II)
12. Expressive vocabulary 13. Verbal reasoning 14. Receptive language 15. Speeded naming	Language	12. Similarities (WASI) 13. Vocabulary (WASI) 14. Comprehension of Instructions (NEPSY II) 15. Speeded Naming (NEPSY II)
16. Internalizing behaviors 17. Externalizing behaviors 18. DSM-oriented behaviors 19. Adaptive behavior function	Behavior	16. CBCL Internalizing Scale 17. CBCL Externalizing Scale 18. CBCL. DSM-oriented Scales 19. ABAS II