A Pilot Study of Optic Nerve Ultrasound Following Cardiopulmonary Bypass

NCT03757312

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THC Pilot Research Program

COVER PAGE

Title of Research Project: Optic nerve ultrasound and CPB; Pilot Study

Principal Investigator (PI):
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Other Personnel

	Name	**Title**
Co-investigator	Joseph Tobias*	MD

* Dr. Tobias is one of the faculty member of CTICU

Proposed start date: November 1, 2018

Proposed end date: November 1, 2019

IRB and/or IACUC Approval: Yes

If Yes, Approval Date: Pending

Additional Information (<u>does not influence score</u>):

Is the project related to the LAUNCH initiative? No

Is there a related QI project? Yes No

Total budget requested: $ 2250

Please include copy of eGrant/eTRAC budget

Abstract (300 words maximum)**:** Despite advances in surgical, anesthetic, perfusion, and nursing care, adverse neurological consequences may occur following cardiac surgery and cardiopulmonary bypass. Consequences of the physiologic effects of cardiopulmonary bypass (CPB) may alter intracranial pressure in the immediate postoperative period. Furthermore, it is suspected that this increase is proportionately greater in patients who undergo procedures involving a direct anastomosis of the superior vena cava to the pulmonary artery (Glenn shunt). The purpose of this study is to evaluate the effects of cardiac surgery and CPB on the central nervous system. Specifically, this study will be looking for the presence of increased intracranial pressure postoperatively by measuring optic nerve sheath diameter (ONSD) using ultrasound. Optic nerve ultrasound has been shown to be effective in the ICU and emergency room setting for detecting increased intracranial pressures and is an accepted standard for such measurements. Each subject will have four optic nerve ultrasound measurements: immediately after the induction of anesthesia, at completion of the surgical procedure after weaning from CPB, prior to leaving the operating room, and on postoperative day one. The findings will be correlated with the following data: age; weight; gender; diagnosis; transfusions; intravenous fluid administration; vasopressors; daily pain scores; narcotic use and amount: analgesic adjuncts; daily vital sings and cerebral near-infrared spectroscopy; arterial blood gases, complete metabolic panels, lactate, and complete bloods counts as per OR and ICU routine.

PROPOSAL: The proposal must include the following sections:

Background and Significance: Despite advances in surgical, anesthetic, perfusion, and nursing care, adverse neurological consequences still occur following cardiac surgery and cardiopulmonary bypass. Consequences of the physiologic effects of cardiopulmonary bypass (CPB) may alter the integrity of the blood-brain barrier and alter intracranial pressure (ICP) in the immediate postoperative period. The potential for ICP increase may be proportionately greater in patients subjected to higher than normal physiologic central venous pressures such as those who undergo procedures involving a direct anastomosis of the superior vena cava to the pulmonary artery (Glenn shunt).

Questions remain regarding the etiology, identification, and prevention of neurological damage following CPB and cardiac surgery. The post-CPB period may be characterized by hemodynamic instability requiring inotropic support and volume resuscitation. While postoperative respiratory and hemodynamic instability may occur, these are generally transient with limited long term implications. However, various factors may impact central nervous system (CNS) function during the perioperative period with the potential for long term sequelae related to neurocognitive impairment. The etiology of such events is multifactorial.

While it is commonly held that the blood brain barrier protects the brain from major intravascular and intracellular fluid shifts, animal data suggest that the blood-brain barrier is impaired with increased permeability following CPB. These changes may result in cerebral edema and increased ICP. While these changes occasionally result in clinically significant effects, it is likely that more subtle changes may occur without clinically apparent effects. The purpose of the proposed study is to evaluate the incidence of subtle increases in ICP following CPB using optic nerve sheath diameter (ONSD), measured by non-invasive ultrasound. As direct measurements of ICP are not feasible following CPB, ONSD will be used as a correlate of ICP. ONSD has been shown to be effective in the ICU and emergency room setting for detecting increased ICP and is an accepted standard for such measurements. Our primary hypothesis is that changes in ICP occur following CPB without clinically appreciable signs and

symptoms. If there is a significant incidence of sub-clinical cerebral edema and increased ICP postoperatively, these findings may impact postoperative hemodynamic and ventilation goals and techniques.

Clinical Impact: An improved understanding of the effects of open-heart surgery and CPB on the intracranial homeostasis may help in the improvement of postoperative care by allowing earlier identification of alterations in ICP that may impact the perioperative course. The post-bypass period may be characterized by hemodynamic and respiratory compromise which may further affect CNS function and outcomes.

The periopra vulnerable state and delayed emergence from anesthesia, delirium, and stroke add significant immediate and long term morbidity and mortality. Since the perioperative ICP change may reflect neurocognitive damage after cardiac surgery and acquiring it will lead to better post-operative analgesia management, which is the key factor for preventing confound respiratory dysfunction, both with inadequate and over aggressive medication.

Second, for evaluating ICP, we will measure ONSD by using ultrasound which has emerged as a viable alternative to quantify increased intracranial pressure. Ultrasound is comparatively cheaper than MRI and CT, non-invasive, and can be done at the bedside in a brief amount of time. Optic nerve ultrasound has been shown be effective in the ICU and emergency room setting for detecting increased intracranial pressures and is an accepted measurement modality. Its use has not been described in the setting proposed here, but it is our hypothesis that it can be used to quantify/describe changes in intracranial pressure after cardiopulmonary bypass. This method could be an effective and practical way to measure ICP in our daily practice.

Specific Aims/Objectives - *State the broad, long-term objectives. Concisely describe what the specific research is intended to accomplish. List the hypothesis to be tested and the project aims. Outline the experimental design and the procedures necessary to accomplish the specific objectives. Discuss any potential limitations with the proposed research. (2 pages maximum)*

Our objective is to better understand the effects of open-heart surgery on the brain by using a novel and simple technique. As our hypothesis, 1.cardiopulmonary bypass during cardiac surgery may influence intracranial pressure and 2. Its change may be measured by ONSD using ultrasound.

As our primary aim, we will test whether ONSD increases after the procedure, as compared to the post-induction baseline. As our secondary aim, we will explore (a) association of elevated ONSD with postoperative outcomes, (b) association of change in ONSD with postoperative outcomes, and (c) persistence of elevated ONSD on POD1.

In this initial pilot study, we will enroll patients aged from newborn to 18 years and will include all congenital heart defects necessitating cardiopulmonary bypass to palliate or repair. The study has been approved by the institutional review board at Nationwide Children's Hospital and the consent of the study will be obtained from patient's parents or legal guardians. In each patient we shall obtain the following data: age; weight (pre-op, upon presentation to ICU, post-op day 1); gender; diagnosis; time to extubation; re-intubations; transfusions (intra-op, post-op days zero, one, and two); intravenous fluid (intra-op, post-op days zero, one, and two); pressors (epinephrine, milrinone, norepinephrine, vasopressin, dobutamine, dopamine); daily pain scores; narcotic use and amount; analgesic adjuncts (acetaminophen and ketorolac); daily vital

signs and cerebral near infrared spectroscopy; arterial blood gases, complete metabolic panels, lactate, and complete blood counts as per OR and ICU routine. In addition, we shall take four optic nerve ultrasound measurements to measure ONSD: immediately after induction of anesthesia, at completion of surgical procedure and prior to leaving the operating room, and the morning of post-operative day one. Measurements will be done by anesthesiologists or research team members who have an experience of ONSD measurement. For the feasibility of ultrasound measurement, we will consider to obtain the data below. For these the time to ultrasound completion and the level of patient cooperation using a 5-point Likert scale (1 = very cooperative to 5 = very uncooperative).Ocular US is going to be performed using a Sonosite (SonoSite Inc., Bothell,WA) machine with high frequency linear probe. We define elevated ONSD 4.0 mm at ages <1 year and 4.5 mm at ages 1-18 year by referring to previous reports. We will use a paired t-test to evaluate change in ONSD after procedure completion, with the confidence level set at 95%. To account for potential non-linearity of ONSD values and the need to use a non-parametric test (sign-rank test) should be considered.

As a potential limitation, patients are not co-operative for measuring ONSD, especially after extubation.

Power Analysis and Biostatistical Analysis Plan – *Provide the power analysis that supports the sample size chosen or explain why a power analysis could not be done. Concisely describe the biostatistical analyses that will be performed and the rationale for the models chosen. (1/2 page estimated length, maximum 1 page). Please include name of biostatistician, if consulted.*

We powered the study to detect an expected magnitude of change in ONSD comparing the post-procedure measurement to the post-induction baseline. A previous study in pediatrics estimated an average ONSD of 3.4 ± 0.7 mm among patients without elevated ICP. Previous reports of acute intraoperative change in ONSD described an increase of 1.1 mm in an adult undergoing transplantation, an average increase of 0.6 mm associated with hypercarbia in adults, and an average increase of approximately 0.2 mm (60 mmHg induced increase in ICP multiplied by .0034 mm average increase in ONSD per 1 mmHg increase in ICP) in an animal model. We propose to use a paired t-test to evaluate change in ONSD after procedure completion, with the confidence level set at 95%. Assuming a moderate correlation of 0.5 between the two ONSD measurements in the OR, the study would achieve 80% power for demonstrating a 0.6 mm increase in ONSD from a baseline of 3.4 ± 0.7 if at least 13 patients are enrolled. To account for potential non-linearity of ONSD values and the need to use a non-parametric test (sign-rank test), we propose to enroll a total of 15 patients.

PLANS FOR FUTURE RESEARCH:

Project timeline:
Obtaining data 2019/1/1-2019/3/31
Analysis 2019/4/1-2019/4/31
Presentation or Paper 2019/10-2020/3

Plans for Extramural Funding - please include expected role for Heart Center Investigators in planned submissions. *(Society/Foundation; industry; clinical trial; NIH K- or R-type grant)*

Potential number/types of abstracts, presentations and publications - please include planned authorship role for Heart Center Investigators. *(Emphasis on impact: abstracts: peer-reviewed, oral/poster presentations, national vs. regional meetings; publications - journal reputation, impact factor)*

One to three presentations at American society of anesthesiologist, Society of Pediatric Anesthesia, European association of cardiothoracic anesthesiology annual congress.

Potential publication at Anesthesiology(IF:6.523), Anesthesia&Analgesia(IF:3.463), Pediatric Anesthesia(IF:2.389),Journal of cardiothoracic and vascular anesthesia (IF:1.574)

BUDGET JUSTIFICATION
(as per items listed in provided eGrant/eTRAC budget)

Personnel:
Statistician Time: Initial 2 hours-$250-
Final:10 hours-$1250-

Patient Costs (requires feasibility review and approval from NCH Clinical Research Services):

Ophthalmic ultrasound(including the cost of the probe cover)
- 4 times per subject, 15 subject total= $1000

Supplies: