JOURNAL of MAINE MEDICAL CENTER

Journal of Maine Medical Center

Volume 1
Issue 1 *Volume 1, Issue 1 (July 2019)*

Article 19

2019

Costas T. Lambrew Research Retreat at Maine Medical Center - Abstracts from 2019

Follow this and additional works at: https://knowledgeconnection.mainehealth.org/jmmc

 Part of the Medicine and Health Sciences Commons

Recommended Citation

(2019) "Costas T. Lambrew Research Retreat at Maine Medical Center - Abstracts from 2019," *Journal of Maine Medical Center*: Vol. 1 : Iss. 1 , Article 19.
Available at: https://knowledgeconnection.mainehealth.org/jmmc/vol1/iss1/19 https://doi.org/10.46804/2641-2225.1024

The views and thoughts expressed in this manuscript belong solely to the author[s] and do not reflect the opinions of the Journal of Maine Medical Center or MaineHealth.

This Supplement is brought to you for free and open access by Maine Medical Center Department of Medical Education. It has been accepted for inclusion in the Journal of Maine Medical Center by an authorized editor of the MaineHealth Knowledge Connection. For more information, please contact Dina McKelvy mckeld1@mmc.org.

Maine Medical Center
MaineHealth

The Costas T. Lambrew Research Retreat is an annual gathering celebrating the accomplishments of a diverse group of students, trainees, faculty, scientists, statisticians and others from a wide range of disciplines including Medicine, Nursing, Nutrition, Social Work, Public Health, Education and many others. This year, researchers from across MaineHealth, the University of Southern Maine, the University of New England, and several other institutions submitted abstracts describing their work in basic/translational, clinical/population health, quality improvement, and health professions education categories. The abstracts below were chosen as winners in their respective categories, with selections from both trainees and faculty for each. We are pleased to present this work and are grateful to have had the opportunity to come together on May 1 as a community to foster collaboration and nurture our scholarly environment.

Feasibility of a lifestyle change group medical visit in primary care

Booth Dargis, Julie Schirmer, Theodore Wissink, Family Medicine

- **Purpose**: Group medical visits have been used in clinical practice for the past 30 years in a wide variety of medical settings. They are primarily employed in chronic disease management such as diabetes mellitus types 1 or 2, asthma, cardiac rehabilitation, and medication assisted therapy for opiate addiction. Further, group medical visits have been effective in routine preventive care such as well child checks and prenatal care. Group medical visits in the above settings have demonstrated similar efficacy to individual care, with added benefits of improved provider and patient clinical experience, and improved provider efficiency. Given these benefits, the group medical visit model is increasingly being adopted in many practice settings throughout the country. Little information is published regarding implementing group medical visits in a general adult primary care or residency training setting, and similarly little is published regarding group medical visits to address general wellness and behavior change. In this retrospective analysis, we propose to examine the feasibility of a Mindfulness Based Therapeutic Lifestyle Change (MB-TLC) group medical visit in a primary care setting.
- **Method/Approaches**: The project is currently under IRB review for exemption. Participants were recruited to Mindfulness Based Therapeutic Lifestyle Change group sessions occurring at two primary care sites over three years. Each series consisted of 8-12 two hour sessions. The MBTLC format is an experiential program that focuses on habit improvement in multiple lifestyle areas. Enrollment, session attendance, and participant BMI and blood pressure were tracked as part of clinical care. We are conducting chart reviews to obtain BMI and blood pressure values at baseline and at the final class. Paired t-tests will be used to compare BMI and vital signs pre vs. post participation.
- **Results**: A total of 175 participants enrolled in the MB-TLC program from 4/2015 to 9/2018; 78 enrolled in one of 6 series at an academic Family Medicine Outpatient Center, while 97 enrolled in one of 9 series at a rural Family Medicine Outpatient Center. Of those enrolled, 74% and 85%, respectively, attended at least one session. Of the group attending at least one session, participants at the rural site attended 5.7 out of 8 sessions, while participants at the academic center attended 7.8 out of the 12 class series and 7.1 out of 8 class series. Collection of BMI and blood pressure data is currently in process.
- **Conclusion**: Group medical visits focused on lifestyle change are indeed feasible in academic and rural primary care settings. Shorter series demonstrate improved attendance per session, and are subjectively better for both provider and participant engagement. It is important to recruit more participants than the goal size, as there will be drop out between enrollment and the start of each series. Tools such as EMR referral and physical information handouts aid recruitment. MB-TLC groups are feasible in primary care, both in an academic and rural setting, though there remain many opportunities for development and further study.

https://knowledgeconnection.mainehealth.org/jmmc/vol1/iss1/19
DOI: 10.46804/2641-2225.1024

Outpatient Naloxone prescriptions in adults at risk for overdose in Cumberland County, Maine

David Kispert, Jenny Carwile, Internal Medicine; Kinna Thakarar, Infectious Disease

- **Purpose**: Between 2011 and 2014, the number of drug-related overdose deaths in Maine increased 34%. Pharmaceutical drugs accounted for 89% of these deaths in 2014. In March 2016, the Centers for Disease Control and Prevention (CDC) released a category A recommendation that providers should consider offering naloxone, a reversal agent for opioid intoxication, to adults at risk of opioid overdose. Risk factors include history of overdose, history of substance use disorder, high opioid dosage (≥50 MME/day), or concurrent benzodiazepine use. Adherence of primary care providers to these guidelines has not been investigated.
- **Method/Approaches:** This study was a retrospective chart review of patients who received care at any of five outpatient IM clinics in Cumberland County, ME between April 1, 2016 and August 1, 2017. Patients ≥18 years who met at least one of the CDC criteria for being high-risk for opioid overdose were considered eligible. We calculated means (SD) and percentages for demographic and clinical variables of interest. The electronic outpatient medication lists of all eligible patients were screened for naloxone prescriptions.
- **Results**: A total of 2,190 patients in the five adult IM clinics were considered high risk for opioid overdose. Seventeen of these patients (<1% of study population) were prescribed naloxone as an outpatient. Four percent of the study population had a high dose opioid prescription and none were prescribed naloxone. Patients prescribed naloxone were younger (mean age 44.4 vs. 54.1 years) and more likely to be female (52.9% vs. 42.5%) and Hispanic (11.8 vs. 1.2%) than patients who did not receive a naloxone prescription.
- **Conclusion**: The low rate of naloxone prescribing in this study underscores a gap in the treatment of individuals at high risk for overdose. Education of primary care providers and patients on CDC guidelines may increase naloxone prescribing in high-risk patients.

Journal of Maine Medical Center, Vol. 1 [2019], Iss. 1, Art. 19

Primary cilia of the cardiac neural crest orchestrate critical aspects of ventricular myocardial maturation and postnatal cardiac function

Lindsey A. Fitzsimons[1,2], Adrian M. Moran[3], Kerry L. Tucker[1,2]

[1]Graduate School of Biomedical Science and Engineering (GSBSE), University of Maine, Orono, ME; [2]Department of Biomedical Research, Center for Excellence in Neuroscience, University of New England, College of Osteopathic Medicine, Biddeford, ME; [3]Department of Pediatric Cardiology, Maine Medical Center, Portland, ME

Background & Project Aims

Cardiac neural crest cells (CNCC; **FIGURE 1-A**) display primary cilia, which are tiny, plasma-membrane bound organelles that function to modulate cell signaling, most notably Hedgehog signaling, and which are implicated in both normal heart development as well as congenital heart disease (CHD; **FIGURE 1-B**). CNCC function as one of the major progenitor cell populations contributing to the developing heart and outflow tract. We hypothesized that loss of primary cilia in CNCC would likely impair normal heart development, leading to CHD. **The purpose of our ongoing research is therefore:** 1) to precisely describe and document the CHD's resulting from the loss of primary cilia of CNCC *in vivo;* 2) elucidate the molecular mechanisms (specifically Hedgehog signaling) leading to this phenotype; and 3) characterize the functional, electrophysiological phenotype prior to the onset of perinatal lethality.

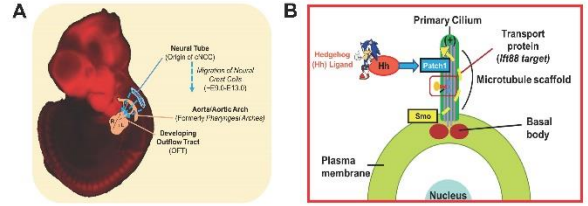


FIGURE 1. Primary cilia of Cardiac Neural Crest Cells (A) CNCC are a neural progenitor population of cells that migrates and contributes to the developing heart. (B) Primary cilia are tiny membrane-bound structures that function as sensory organelles. Many critical developmental signaling pathways involve localization to the primary cilium, most notably, Hedgehog (Hh) ligand and it's receptor, Patch1. The *Smoothened* (Smo) receptor is essential for downstream Hh signal transduction, where it localizes to the cilium following Hh binding to Patch1.

Research Design & Methodology

To model the pathogenesis of CNCC-specific ciliary loss, we utilized a Wnt1:Cre-2, Ift88-targeted conditional elimination of primary cilia, and a Td-Tomato reporter to track CNCC migration (**FIGURE 2-A**). To investigate potential roles of Hedgehog signaling in myocardial maturation of Ift88-homozygous mutants, we expressed a constitutively-active Hedgehog receptor, Smoothened-M2 (Smo-M2) in CNCC (**FIGURE 2-B**).

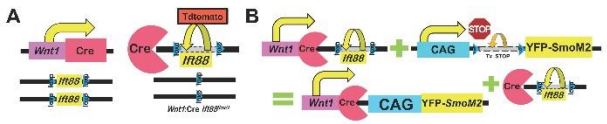


FIGURE 2. ***In vivo*** **elimination of primary cilia of neural crest cells using multiple neural crest-specific Cre drivers.** (A) *Wnt1*:Cre-1 (Danielian *et al*, 1998); *Wnt1*-Cre-2 (Lewis *et al*, 2013); *Ift88* conditional knockout (Haycraft *et al*, 2007); Tdtomato reporter (Madisen *et al*, 2010); (B) Additional *in vivo* investigation Hedgehog signaling using *SmoM2* (R26SmoM2; Jeong *et al*, 2004) in CNCC

Results

I. LOSS OF PRIMARY CILIA IN CNCC LEADS TO A VARIETY OF CHD

The phenotype resulting from loss of primary cilia in CNCC was characterized by a variety of outflow tract defects, ventricular-septal defects (VSD), disorganization of the ventricular endocardium, pronounced noncompaction of the ventricular myocardium, and perinatal lethality (**FIGURE 3**). Diagnostically-significant noncompaction was identified when the ratio of trabecular to compact thickness exceeded 2.0.

A Td-tomato reporter mouse was used to track migration of CNCC, quantify the loss of primary cilia and examine the developing myocardium/endocardium (**FIGURE 4**). We observed the loss of primary cilia in CNCC beginning at embryonic day E9.5. Notably, CNCC contribution to the ventricular myocardium was observed along with pronounced disorganization of the endocardium visible by E10.5 (**FIGURE 4-5, 7**). This outcome represents a particularly novel aspect to the project, as neural crest cells have not historically been thought to contribute to the ventricular myocardium.

Results

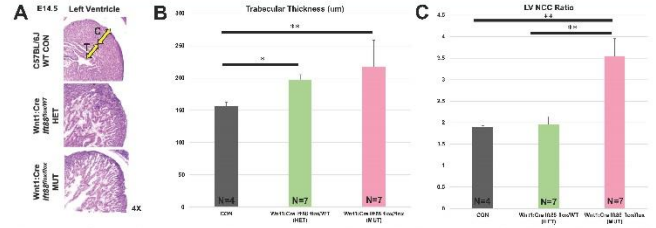


FIGURE 3. Quantification of noncompaction of the ventricular myocardium resulting from loss of cilia from CNCC at E14.5 (A) Paraffin-embedded, transverse cross sections of wild-type control (WT CON;C57BL/6J), heterozygous (HET Cre+/Ift88$^{flox/+}$) and *Ift88* conditional knockout mutant embryos (MUT; Cre+/Ift88$^{flox/flox}$) stained with standard hematoxylin and eosin (H&E) at embryonic time point E14.5. (B-C) Comparison of mean left ventricular trabecular thickness and mean left ventricular trabecular:compact thickness (LV NCC Ratio) in CON, HET, and MUT Ift88 CKO mice, respectively. *Indicates statistically significant differences ($p< 0.05$); **($p< 0.01$).

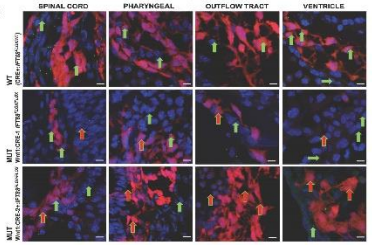


FIGURE 4. Use of Td-tomato (Tdt) reporter to track cardiac neural crest migration, location and ciliation of both Wnt1:Cre embryos at E10.5. Confocal analysis of (Tdt+/Cre+) cells in the spinal cord, pharyngeal arch, outflow tract and ventricular regions of the developing embryo. Tdt+/Cre+; αAr13B (Primary Cilia); DAPI (Nuclei);images acquired using confocal microscopy (Leica Microsystems) using a 63X objective with a zoom factor of 3.0) Indicates any cell with an intact primary cilium; Indicates Tdt+/Cre+ cells where an intact primary cilium is no longer present.

II. QUANTIFICATION OF LOSS OF PRIMARY CILIA IN CNCC

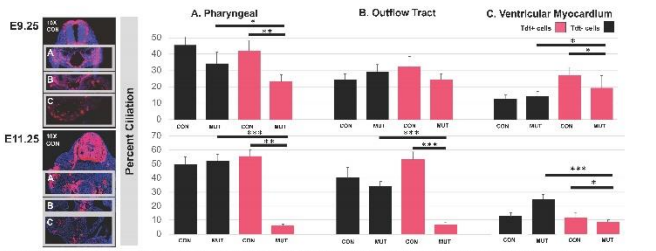
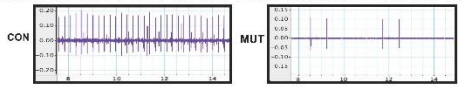


FIGURE 5. Quantification of loss of cilia from CNCC during early heart development. Percentage of intact cilia on Td-tomato-positive (Tdt+/Cre+/CNCC) cells began to decrease at E9.25 in the MUT in both the pharyngeal (A) and ventricular myocardial (C) regions (top panel). Pronounced loss of cilia of CNCC was evident by E11.25 in pharyngeal, outflow tract and ventricular myocardial regions (A-C; bottom panel). *Indicates statistically significant differences ($p< 0.05$) when comparing CON (Wnt1:Cre-2+/*Ift88*$^{flox/+}$; n=3) to MUT (Wnt1:Cre-2+/*Ift88*$^{flox/flox}$; n=4); **$p\leq0.01$;***$p\leq0.001$.

III. PERINATAL LETHALITY & ELECTROPHYSIOLOGICAL DEFECTS



Mouse Line	AVC HR (bpm)		P-R (ms)		QRS (ms)		QRS Amp (mV)	
Wnt1:CRE-2 Ift88 *flox*	CON	MUT	CON	MUT	CON	MUT	CON	MUT
	149±7.0	32±12.8**	41.21±0.45	N/A	0.016±0.02	0.019±0.03	0.50±0.11	0.89±0.11*

FIGURE 6. Non-invasive electrocardiography (ECG) and electrophysiological assessment optimized for newborn mice during the first postnatal day (P1.0). Electrophysiological assessments of Wnt1:Cre-2/Ift88 newborn mutants (MUT; N=7) revealed bradycardia, conduction defects, and ECG tracings consistent with ventricular hypertrophy when compared to littermate controls (CON; N=8). Means are ± SD; ***Indicates statistical significance of Student's T-test, $p < 0.001$; *Indicates statistical significance $p < 0.01$; *$p<0.05$.

Results

IV. LOSS OF PRIMARY CILIA OF CNCC DISRUPTS ENDOCARDIAL DEVELOPMENT

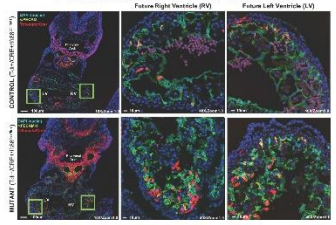


FIGURE 7. Loss of primary cilia in CNCC leads to endocardial disorganization during early development of the ventricle myocardium. Noticeable disorganization of the ventricular endocardium was observed in MUT embryos at E10.5 when compared to littermate controls (CON). Disorganization to the endocardium refers to the obvious disruption in signal, creating a discontinuous and non-linear arrangement of the endocardial cells of the MUT when compared to CON. Notable contribution from Tdt+cells to the ventricular myocardium was also evident by E10.5.Tdt+/Cre+; αPECAM/CD-31 (Endothelial cells); DAPI (Nuclei)

V. PERTURBATION OF HEDGEHOG SIGNALING & VENTRICULAR MATURATION

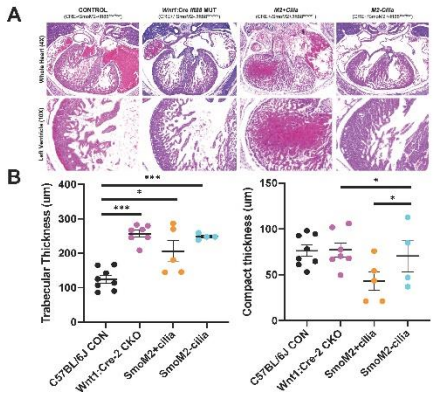


FIGURE 8. Noncompaction of the ventricular myocardium persists with the expression of *Smo-M2*. (A-B) Hypertrabeculation was observed, regardless of the presence of *Smo-M2* expression in *Ift88*-homozygous mutants. Notably, expressing *Smo-M2* background resulted in severe reduction of compact ventricular thickness, an observation not seen in the original *Wnt1*:Cre-2/*Ift88* mutant phenotype (A-B). This novel effect confirms out hypothesis that that proper Hh signaling is in fact, dependent on the presence of primary cilium itself. ***Indicates statistical significance $p \leq 0.001$; **$p \leq 0.01$; *$p\leq0.05$.

Conclusions & Acknowledgements

PRIMARY CILIA OF CNCC & PATHOGENESIS OF CHD

1) CNCC contribute to ventricular myocardium of the developing mouse heart; this phenomenon is not dependent upon the presence of primary cilia in CNCC
2) Loss of primary cilia in CNCC leads to OFT defects, VSD, impaired ventricular maturation (NCC) and perinatal lethality
3) Primary cilia of CNCC are essential to healthy heart development

HEDGEHOG SIGNALING, CNCC & PATHOGENESIS OF CHD

1) These data collectively support a critical role for primary cilia and dose-dependent Hedgehog signaling in the development of the ventricular myocardium as well as in the pathogenesis of CHDs.

https://knowledgeconnection.mainehealth.org/jmmc/vol1/iss1/19
DOI: 10.46804/2641-2225.1024

Delayed Initiation of Therapeutic Hypothermia for Outborn Infants is Associated with Adverse Outcomes

Nabeel Hashmi[1], MS4, Max Sale[2], MD, Leah Fox[2], MD, Jay Kerecman[3], MD, Lauren McAllister[1], MS4, Misty Melendi[2], MD, Frances L. Lucas[2], PhD, Alexa Craig[2], MD

Tufts School of Medicine[1], Boston, MA; Maine Medical Center[2], Portland, ME; Northern Light Eastern Maine Medical Center[3], Bangor, ME

Background/Aims

- Neonatal Encephalopathy (NE) is a clinical syndrome affecting between 2-5 per 1000 live births. Therapeutic hypothermia (TH) is a neuroprotective treatment for NE
- In Maine, the majority of infants who meet eligibility criteria for TH are born in community hospitals (outborn) and must be transferred to a tertiary care center for treatment
- **Aim:** Characterize time to TH initiation for infants born in tertiary care centers (inborn) versus outborn infants and determine if delayed initiation is associated with adverse short-term outcomes

Methods

- Retrospective study of infants treated with TH between 2008 and 2018 in two NICUs excluding infants older than 6 hours at TH initiation (14), less than 35 weeks gestational age (5), early termination of TH (1), absence of encephalopathy (2), and no MRI (11)
- MRIs scored by blinded neuroradiologist using the Weeke* scoring system with severe injury defined as grey matter score >9.5 * Weeke et al (2018), doi:10.1016/j.jpeds.2017.09.043
- Primary outcome: Time to initiation of TH compared between inborn and outborn infants
- Secondary outcome: In-hospital mortality, severe MRI injury and/or severe seizure on EEG defined as use of phenobarbital, fosphenytoin and midazolam drip
- Statistical analysis: Baseline differences between inborn and outborn infants were compared using chi square or Fisher's exact tests for categorical variables and t-tests or their non-parametric equivalents for continuous variables. Logistic regression was used to control for confounding

Table 1. Clinical/Demographic Characteristics*

	Inborn n= 69	Outborn n= 153	p-value
Maternal Characteristics			
Gestational Diabetes (n, %)	14 (20%)	15 (10%)	0.05
Mean Maternal Age (SD)	30.4 (5.9)	27.6 (5.9)	0.001
Delivery Characteristics			
Cesarean section (n, %)	41 (59%)	79 (52%)	0.35
Chest compressions performed (n, %)	10 (15%)	56 (37%)	0.001
Infant Characteristics			
Female Sex (n, %)	31 (45%)	70 (46%)	0.99
Mean birth weight in kg (SD)	3.3 (0.7)	3.4 (0.6)	0.19
Mean Gestational Age in Weeks (SD)	38.5 (2.0)	39.6 (1.7)	<0.001
Median Apgar Score 1 min (# obtained, IQR)	1 [69, 1, 2]	2 [151, 1, 3]	0.06
Median Apgar Score 5 min (# obtained, IQR)	4 [69, 3, 6]	4 [150, 3, 5]	0.70
Median Apgar Score 10 min (# obtained, IQR)	6 [55, 4, 7]	6 [135, 4, 7]	0.53
Cord Gases			
Number of arterial gases obtained (n, %)	55 (80%)	88 (58%)	0.002
Mean arterial pH (SD)	7.04 (0.16)	7.06 (0.18)	0.48
Number of venous gases obtained (n, %)	52 (75%)	82 (54%)	0.003
Mean venous pH (SD)	7.10 (0.17)	7.13 (0.20)	0.47

*Statistically insignificant differences in characteristics not shown here include maternal fever, GBS positive, pre-eclampsia/eclampsia, vacuum assistance, shoulder dystocia, nuchal cord, cord prolapse, placental abruption, uterine rupture, late decelerations on fetal heart monitoring, chorioamnionitis, and prolonged rupture of membranes

Grey Matter Injury on MRI

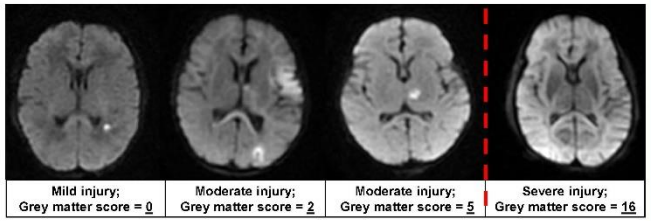
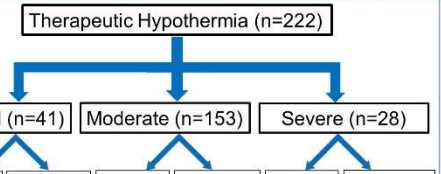


Table 2. Outcomes

All infants	Inborn n= 69	Outborn n= 153	p-value
Median Hour of Life TH Initiated (IQR)	1 (1,3)	4 (3,5)	<0.001
Mortality (n, %)	3 (4.3)	21 (13.7)	0.038
Any seizure (n, %)	16 (23.2)	57 (37.5)	0.045
Severe seizure (n, %)	3 (4.3%)	14 (9.2%)	0.28
Severe grey matter injury (n, %)	2 (3)	8 (5.7)	0.62
Mortality, severe seizure, and/or severe grey matter injury (n, %)	7 (10.1)	34 (22.2)	0.039

Results: Encephalopathy Tree Diagram



	Inborn (n=9)	Outborn (n=32)	Inborn (n=52)	Outborn (n=101)	Inborn (n=8)	Outborn (n=20)
Median Hr of life TH initiated (IQR)	4 (1.5, 4.5)	4.1 (3.5, 5)	1 (1, 2.5)	3.5 (3, 4.5)	1 (0.9, 1.6)	3 (2.4, 5)
	p=0.57		p<0.001		p=0.002	
Death, severe seizure, and/or severe grey matter injury (n, %)	0 (0%)	1 (3.1%)	3 (5.8%)	14 (13.9%)	4 (50%)	19 (95%)
	p=1.00		p=0.18		p=0.02	

Table 3. Logistic Regression Analysis

Assessing Effect of Confounding on Combined Outcome of Mortality, Severe Seizure, or Severe Grey Matter Injury on MRI

	Predictor Variable	Odds Ratio	95% C.I.
Parent Model	Outborn infant	2.53	1.11-6.52
Extended Model*	Outborn infant	4.95	1.57-20.0

*Extended model is controlling for confounding from encephalopathy severity, gestational age, gestational diabetes and sex

Conclusions

- There is significant delay in TH initiation for outborn infants and an associated increase in the odds of death, severe neonatal seizures and/or severe grey matter injury.
- The relationship between delayed TH initiation and severe adverse outcomes is strongest for those with symptoms of severe encephalopathy.
- Investigation into factors contributing to severe encephalopathy prior to and immediately following birth is urgently needed.

Acknowledgments

Thank you to Adam Black for support and guidance with Rstudio, to Scott Evans, RN for help with NICU data collection and to Eric Frehm, M.D. for his editorial contributions. Financial support for this project was provided by the Northern New England Clinical and Translational Research Institute Pilot Study Program.

The effect of beta blocker use on bone outcomes using the Framingham Osteoporosis Study

Journal of Maine Medical Center, Vol. 1 [2019], Iss. 1, Art. 19

Christine Lary, Alexandra Hinton, Center for Outcomes Research & Evaluation; Kathleen Nevola, Tufts University;
Theresa I. Shireman, Andrew R. Zullo, Brown University; Katherine Motyl, Center for Molecular Medicine; Karen L. Houseknecht, UNE;
F. Lee Lucas, Sarah Hallen Center for Outcomes Research & Evaluation; Sarah D. Berry, Harvard Medical School

- **Purpose**: Beta Blockers (BBs) have shown positive effects on bone mineral density (BMD) and fracture outcomes in several studies, with some but not all finding increased effect for Beta-1 selective BBs. It is unresolved how Beta-1 selectivity influences this effect and how the effect varies by skeletal site. Our objective was to test the hypotheses that 1) BB use and 2) Beta-1 selective BB use are associated with greater hip and spine BMD and lower incidence of osteoporotic fractures.
- **Method/Approaches:** We used data from the Offspring (2nd generation) cohort of the Framingham Heart Study (N=2,803), a prospective study of cardiovascular outcomes. BB use and Beta-1 selective BB use and covariates were assessed between 2005-2008, which was the index date. Femoral neck (FN), trochanter, total femur, and lumbar spine (L2-L4) BMD were measured using dual energy x-ray absorptiometry in cohort members willing to return for a call back visit (N=1662). Occurrence of an osteoporotic fracture between the index date and the end of follow-up (August 2013) was noted. Covariates were age, height, weight, current smoking, cigarettes per day, prior cardiovascular disease, current treatment for diabetes, hypertension, hyperlipidemia, and menopause and hormone therapy for women. Analyses were done for the full cohort and stratified by sex, and models were adjusted for covariates using linear or logistic regression for BMD or fracture.
- **Results**: Of the 1,662 who participated in the Osteoporosis study visit (53.1% female, average age 66), BB were used by 418 (25.2%) individuals, 358 (85.6%) of which were B1-selective users, with atenolol and metoprolol being the most common medications. FN BMD was significantly higher in BB users vs. non-users in crude and adjusted sex-combined models (0.019 g/cm2 greater; 95% CI 0.003-0.035, p=0.0171 in adjusted model). The effect of Beta-1 selective agents was similar (0.017 g/cm2 greater; 95% CI 0.001-0.033, p=0.0399). Sex-stratified models showed similar trends but were not significant. Other BMD sites showed significant results in crude but not adjusted models. Of the full cohort of 2,803, 204 (7.3%) had an osteoporotic fracture, 61 (8.4%) for BB users and 143 (6.9%) for non BB-users. There was no significant association between BB use and fracture in either crude or adjusted models (odds ratio of 1.09; p=0.6758 in adjusted model).
- **Conclusion**: BB use and B1-selective BB use were significantly associated with higher BMD of the hip, but there was no reduction in risk for incident fractures among users. This may due to insufficient influence of BMD to reduce fracture risk, or because BBs may affect other fracture risk factors such as falls.

https://knowledgeconnection.mainehealth.org/jmmc/vol1/iss1/19
DOI: 10.46804/2641-2225.1024

Maine Medical Center
MaineHealth

Comparison of intraoperative tranexamic acid and epsilon-aminocaproic acid in cardiopulmonary bypass patients: a natural experiment

Michael Robich, Robert Kramer, Cardiac Surgery; Patrick Grant, Mark Broadwin, Cardiology;
Igor Prudovsky, Center for Molecular Medicine; Robert Groom, Cardiology, Joseph Rappold, Cardiac Surgery

- **Purpose**: The lysine analogs tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA) are the most commonly used antifibrinolytic agents in patients undergoing cardiac surgery with cardiopulmonary bypass. Previous studies have shown variable outcomes when comparing the two agents. A retrospective review was completed to ascertain if there is a benefit to utilizing TXA in substitution of EACA during the intra-operative period of patients undergoing cardiac surgery with cardiopulmonary bypass.

- **Method/Approaches:** We were given an opportunity to explore the relative efficacy of TXA and EACA when in May 2013 to June 2014 an EACA shortage necessitated substituting TXA creating a natural contemporary comparison. The substitution of TXA for EACA created an opportunity to analyze a natural experiment (see Craig et al. Natural Experiments: An Overview of Methods, Approaches, and Contributions to Public Health Intervention Research. Annual Review of Public Health 2017 38:1, 39-56). Patients included were operated on between May 2013-June 2014 (when TXA was utilized), and between June 2014-May 2015 (when EACA was utilized). Included in this study were patients greater than 18 years old who underwent procedures that required CPB during both time periods, and received either TXA or EACA intra-operatively. Any subject who did not meet the aforementioned criteria, who underwent off-pump surgery, did not have an antifibrinolytic agent administered, or had a known history of a coagulation disorder were excluded. 845 adult cardiac surgery patients who received TXA during the shortage period were compared with 777 patients who received EACA after the shortage. Primary outcomes were hospital mortality (index admission), stroke, acute kidney injury using the AKIN (Acute Kidney Injury Network) definition, need for reoperation, post-operative chest tube output within 24hrs, all blood products received (intra-operatively and post-operatively), and seizures. Secondary outcomes were post-operative length of stay, intensive care unit length of stay, total post-operative ventilation hours, and cost of hospitalization. The majority of data was collected from a prospectively maintained cardiac surgery database as defined by the Society of Thoracic Surgeons (STS). Information that was not present in the database was manually abstracted through chart review in the electronic medical record (EPIC Systems Corp., Verona, WI) by the co-investigator and the research coordinator. The finance department compiled the economic data from which charges and cost were derived. They extracted all services using chargemaster codes with the date of service, revenue code, charge and related expense utilizing the cost accounting and budgeting software StrataJazz. All services were cross-referenced to the medical record number and date of surgery at which point all services provided after the date of surgery were accounted for in the charge and cost summary. Patient population and lab values were described using proportions for categorical variables and means and standard deviations or medians and ranges, as appropriate, for continuous variables. We assessed differences in outcomes between study groups using t tests; when data were not normally distributed, we performed appropriate transformations or non-parametric tests to make these comparisons.

- **Results**: TXA use was associated with a lower overall transfusion rate [OR 0.81 (95% CI 0.66 to 0.99)] mainly because of the significant difference in platelet transfusions. Patients who received TXA were statistically less likely to receive platelets [OR 0.50 (95% CI 0.36, 0.68)]. However, they were not statistically less likely to receive red blood cells (RBC) [OR 0.81 (95% CI 0.66, 1.00)] or fresh frozen plasma [OR 0.86 (95% CI 0.63, 1.17)] as the confidence interval contained the referent of one. There was no statistical difference with respect to stroke, mortality, reoperation for bleeding, chest tube drainage, and AKI. As a result of the low incidence of seizures in both cohorts, one seizure in EACA and zero seizures in the TXA cohort, we can state that there did not appear to be an increased risk of seizure when comparing TXA to EACA. Secondary outcomes results were adjusted for clopidogrel use and previous cardiac surgery using the EACA cohort as the referent and expressing mean difference followed by confidence limits for each cohort: Post-operative length of stay [mean difference of -1.1 days (95% CI -1.7 to -0.4)], intensive care unit length of stay [difference of -9.3 hours (95% CI -17.5 to -1.1)], ventilator time [difference of -17.2 hours (95% CI -26.8 to -7.5)], and average post-surgical cost per patient: TXA $18,583; EACA $21,972 (p = 0.05), a difference of $3,389.

- **Conclusion**: TXA outperformed EACA as the antifibrinolytic drug during cardiac surgery with CPB as several outcomes were significantly better in TXA-treated patients than in those treated with EACA. TXA was associated with fewer platelet transfusions, less postoperative ventilator time, shorter intensive care unit and postoperative length of stay, and lower cost without an increase in mortality, stroke, reoperation for bleeding, AKI, or seizures. This analysis favors the use of TXA when compared with EACA as the antifibrinolytic during cardiac surgery with cardiopulmonary bypass. TXA is a safe, cost-effective treatment modality and should be considered when selecting an antifibrinolytic agent for patients undergoing CPB.

Wellness in teaching: a dynamic educational intervention to improve faculty performance

Sue Rose, Medical Education; Vicki Hayes, Bryan Lamoreau, Amy Segdwick, Christine Hein, Family Medicine

- **Purpose**: For providers in an academic setting, there are expectations for teaching and research that can add stress to the emotional demands of clinical practice. There is scarce data for the role of curricula aimed at prevention of burnout in academic clinicians. The objectives of this curriculum were to educate faculty on wellness theories and tools to specifically improve flow, mindfulness, and resilience. By the end of the course participants should be able to analyze their own applications of wellness within their practice.
- **Method/Approaches:** This was a 6-week pilot program containing 3 modules targeting all clinicians and learners in the MaineHealth system with an n=9. Each interprofessional module was 2 weeks in duration consisting of two 2-hour in person workshops consisting of lecture, small group work and question and answer methods that taught the wellness concepts of flow, mindfulness and resilience. The program modules also included regular yoga practice at local yoga studios to reinforce the practical application of these concepts. Participants were asked to practice yoga twice a week at a minimum. Pre and post qualitative surveys and validated scales of these concepts were used to assess the effects of the program. Changes in scores were analyzed using pair t-tests. Two coders conducted the qualitative analysis.
- **Results**: We found four themes emerge in our qualitative data: being more mindful, being less reactive, work/life balance, and applying strategies to teaching. Quantitative analysis of the 3 validated scales showed improved scores in mindfulness, resilience, and flow.
- **Conclusion**: Qualitative themes were consistent with the goals of the course and feedback was overwhelmingly positive. Conscious changes to workflow in the teaching environment were already taking place by the end of the course. Participants reported, one of the main barriers for clinicians participating in the program was securing enough time to commit to the full program. This program increased educators' sense of well-being and teaching self-efficacy; improving ability to manage the learning environment and establish and maintain supportive relationships with learners.

https://knowledgeconnection.mainehealth.org/jmmc/vol1/iss1/19
DOI: 10.46804/2641-2225.1024

Development of 3D adipose tissue organoids to model human perivascular adipose tissue development and dysfunction

Lucy Liaw, Joshua Boucher, Jacqueline Turner, MMCRI Center for Molecular Medicine

- **Purpose**: Perivascular adipose tissue (PVAT) is a critical regulator of blood vessel tone and function. Residing circumferential to the adventitia, PVAT exerts effects on blood vessel phenotype through secretion of vasoactive cytokines in the local environment. In healthy individuals, paracrine release of vasodilatory and anti-inflammatory compounds support normal vascular function and quiescence. Cardiometabolic dysfunction leads to pathological conversion of PVAT and abrogation of its vasoprotective effects, ultimately exacerbating cardiovascular disease (CVD). Of all human PVAT sources, aortic PVAT (hAPVAT) represents a plentiful source of PVAT that is commonly resected and discarded during coronary bypass and other open heart surgical procedures. Despite its availability, human PVAT research remains scarce and mechanisms regulating its dysfunction in patients with CVD have are not characterized. This is likely due to the invasiveness of procurement and the challenges of working with adipose tissue ex-vivo.
- **Method/Approaches:** Given these considerations, we hypothesized that we could develop a multi-cellular, three dimensional (3D) adipose tissue organoid to be used as a physiologically-relevant model for assessing hAPVAT development.
- **Results**: Here we show that adipose progenitor cells (APC) from hAPVAT resected from the ascending aorta of coronary bypass patients can be explanted and propagated, and form 3D micro-tissues when suspended in hanging drop culture. APC-derived micro-tissues successfully differentiate into mature, lipid-storing tissue that express adipose markers PLIN1, FASN and UCP-1. Further, we incorporated human endothelial cells into the organoids and demonstrate formation of capillary structures absent exogenous VEGF-A, suggesting endogenous factors within the adipose organoids support long-term endothelial survival. Differentiated adipose organoids were viable for >2 weeks with prolonged detection of markers of progenitor cells (PDGFRα), pre-adipocytes (PPARγ), mature adipocytes (FABP4) and endothelial cells (VE-CADHERIN), a finding consistent with in vivo adipose tissue and not observed in mono-layer culture. Our lab previously reported that the small trafficking protein RAB27A is a novel regulator of adipogenic differentiation in monolayer cultures. Therefore, we silenced Rab27a in APC prior to forming 3D tissues and observed elevated lipids and adipogenic markers, and loss of endothelial cell survival compared to control, demonstrating the versatility and functionality of adipose organoids for use in mechanistic studies.
- **Conclusion**: Collectively, we have developed a 3D, physiologically-relevant technique for modeling hAPVAT development using progenitor cells from patients with CVD. This application can be expanded for use with APC derived from other human adipose depots and greatly enhances our toolset for studying mechanisms regulating adipogenesis in humans.