18th Annual Safar Symposium

FUTURE VISIONS *for* Neuroprotection Neuroanesthesia & Neurorehabilitation

ABSTRACTS

Multi-Departmental Trainees' Research Day

Wednesday May 19, 2021 | 2 pm to 4 pm | Virtual

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BREAKOUT ROOM 1

Department of Anesthesiology and Perioperative Medicine

Basic Science

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Abstract 1

SEX DIFFERENCES IN PROTEIN KINASE A SIGNALING OF THE LATENT POSTOPERATIVE PAIN SENSITIZATION THAT IS MASKED BY KAPPA OPIOID RECEPTORS IN SPINAL CORD

Basu P, Prasoon P, Taylor B

Department of Anesthesiology & Perioperative Medicine, Pittsburgh Center for Pain Research, and the Pittsburgh Project to end Opioid Misuse, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213

Introduction: Acute postoperative pain is followed by persistent pain in 10-50% of individuals undergoing operations, such as breast, coronary bypass, and thoracic surgery, groin hernia repair, and leg amputation. Although opioids can effectively treat acute postoperative pain, prolonged opioid therapy for chronic postoperative pain is less efficacious and associated with major problems including dependence, addiction liability, and opioid induced hyperalgesia. A better understanding of the cellular mechanisms that drive persistent pain and its opposing endogenous analgesia may lead to the development of novel treatments for chronic postoperative pain.

Hypothesis: The current studies were designed to test the hypothesis that surgical incision establishes a long-lasting activation of kappa opioid receptor (KOR) signaling that masks latent pain sensitization.

Methods: To address this hypothesis, we performed plantar incision in male and female mice, waited for behavioral signs of hyperalgesia to resolve (at least 21 days), targeted KOR with intrathecal injection of selective antagonist, and then evaluated behavioral signs of hyperalgesia and spinal neuronal activation in the dorsal horn. With this model, we recently reported that either of two KOR antagonists, nor-BNI or LY2456302, reinstated hyperalgesia in male mice when administered 3 weeks after incision. Here, we report that LY2456302 reinstated hyperalgesia even when administered 13 months after surgical incision, indicating that chronic pain vulnerability persists for over a year in a latent state of remission. We next determined whether KOR maintains latent postoperative pain in a state of remission by inhibiting N-methyl-D-aspartate receptor (NMDAR)→cAMP-dependent pathways. To this end, we focused on adenylyl cyclase isoform 1 (AC1) and its downstream receptors, protein kinase A (PKA) and exchange protein activated by cAMP (EPAC). We used AC1 knock-out (KO) mice and pharmacological inhibitors or activators of NMDA (MK-801, 1 μg/5 μL, i.t.), AC1 (NB001, 1.5μg i.t.), PKA (H89, 10 nmol; 6-bnz, 10 nmol) and Epac1/2 (ESI-09, 10μg i.t.; 8-cpt, 3 nmol), and measured mechanical stimulus-evoked behaviors and immunoreactivity of phosphorylated extracellular signal-regulated kinase (pERK), a marker of LS-associated sensitization of spinal dorsal horn neurons.

Results: We report that AC1 gene deletion and NB001 prevented LY2456302-evoked reinstatement of hyperalgesia and/or activation of dorsal horn neurons in both sexes. LY2456302 administration increased number of pERK+ in wild type compared to AC1 KO male and female mice. Data showed that MK-801 prevented LY2456302-evoked reinstatement of mechanical hyperalgesia in both male and female mice. H89 prevented LY2456302-evoked reinstatement of mechanical hyperalgesia in male but not female mice, and 6-bnz reinstated postoperative hyperalgesia in male but not female mice. ESI-09 reversed hyperalgesia in both sexes and 8-cpt reinstated hyperalgesia in both sexes.

Conclusions: We conclude that sustained KOR signaling inhibits spinal PKA-dependent mechanisms that drive postoperative LS in a sex-dependent manner.

Significance: Our findings support the development AC1, PKA, and EPAC inhibitors towards a new pharmacotherapy for chronic postoperative pain.

Research/Grant Support: NIH R01DA037621 and R01NS045954 (PI: Bradley K. Taylor, PhD)

Abstract 2

EXAMINATION OF POTENTIAL SIDE EFFECTS OF A NOVEL GLYCINERGIC ANALGESIC FOR TREATMENT OF CHRONIC PAIN

Caporoso J,[1] Jiang L,[1] Tillman TS,[1] Tang P,[1,2,4] Xu Y[1,3,4,5]

Departments of Anesthesiology[1], Computational and Systems Biology[2], Structural Biology[3], Pharmacology and Chemical Biology[4], Department of Physics and Astronomy[5], University of Pittsburgh School of Medicine

Introduction: Glycine receptors (GlyRs) are ligand-gated ion channels that mediate nociceptive signals in the central nervous system. Previously, we presented a novel analgesic (MJPY1) that alleviates thermal hyperalgesia and mechanical allodynia in rodent models of neuropathic and inflammatory pain. MJPY1 is a selective positive allosteric modulator of α3-containing GlyRs and binds specifically to a transmembrane domain site for Δ9-tetrahydrocannabinol (THC), one of the major psychoactive components in cannabis.

Hypothesis: Here, we show that the glycinergic mechanisms of analgesia are independent of the psychoactive effects and modulation of opioid receptors.

Methods: A battery of *in vivo* tests was performed with MJPY1 to assess its selectivity for α3-containing GlyRs, potential for psychomotor side effects, and potential for substance use disorder. To determine if MJPY1's analgesic action is mediated by other analgesic receptors, such as opioid receptors, Sprague-Dawley rats with chronic constriction injury induced-neuropathic pain were treated with MJPY1 in the absence and presence of the opioid receptor inhibitor naloxone. The thermal and mechanical hypersensitivities were assessed by Hargreaves and von Frey tests. Psychomotor side effects were examined using the open field and horizontal ladder rung walking tests in rats without pain conditions. Substance use disorder potential, such as drug seeking and reward behaviors, were investigated using the conditioned place preference test in naïve rats with repeated exposures to MJPY1.

Results/Conclusions: The results of these tests suggest that MJPY1 produces analgesia independent of opioid receptors, does not cause detrimental locomotor side effects, and does not establish substance use conditioning, making MJPY1 an attractive alternative to current chronic pain treatments.

Significance: In conclusion, MJPY1 represents a novel class of analgesics that may transform chronic pain managements in the future.

Research/Grant Support: NIH R01 GM049202 (PI: Prof. Yan Xu, Ph.D.; PI: Prof. Pei Tang, Ph.D.). NIH T32 GM075770 (PI: Xu).

Abstract 3

MEDULLARY KAPPA OPIOID RECEPTOR NEURONS INHIBIT PAIN AND ITCH THROUGH A DESCENDING CIRCUIT

Nguyen E,[1] Smith K,[1] Silberberg H,[2] Cramer N,[3] Le Pichon C,[2] Keller A,[3] Ross SE[1]

[1]Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh School of Medicine
[2]Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health
[3]Department of Anatomy and Neurobiology, University of Maryland, School of Medicine

Introduction: In perilous and stressful situations, the ability to suppress pain can be critical for survival. Although much is known about the role of spinally-projecting medullary neurons in the inhibition of pain, the precise identities and mechanisms of pain-inhibitory neurons have never been identified.

Hypothesis: We tested whether descending inhibitory neurons could inhibit itch and pain at the level of the spinal cord in mice.

Methods: **Mice:** All mice were of the C57Bl/6 background (n = 7-14 mice). Even numbers of male and female mice were used for all experiments. **Chemogenetic manipulations:** The intrathecal space was exposed, and two injections of approximately 300nl of virus (AAVr-hSyn-DIO-hM3D(Gq)-mCherry or control) was injected the spinal cord. Clozapine-N-oxide (Tocris) was dissolved in PBS and administered locally via cannula injection (1mmol in 300nl). **Spared nerve injury:** the sural and superficial peroneal branches of the sciatic nerve were ligated and transected, leaving the tibial nerve intact. **Behavior:** All assays were scored by an experimenter blind to treatment. **Von Frey testing:** Mechanical sensitivity was measured using the Chaplan up-down method. Lifting, shaking, and licking were scored as positive responses to von Frey stimulation. **Hargreaves testing:** A radiant heat source was applied to the hindpaw and latency to paw withdrawal was recorded. To avoid tissue damage, a cut off latency of 20 sec was set. **Stress-induced analgesia:** Mice were placed in a water bath maintained at 30C and forced to swim for 3 minutes. After, mice were returned to their home cages and tested 30 minutes later for stress-induced. **Statistical analysis:** Significance was indicated by $p < 0.05$. Sample sizes were based on pilot data and are similar to those typically used in the field.

Results: The selective activation of spinally-projecting medullary neurons containing the kappa opioid receptor (KOR) resulted in robust suppression of nociception to mechanical and thermal stimuli as well as mechanical sensitivity following acute and chronic injury. Furthermore, activation of KOR neurons significantly inhibited responses to itch. By inhibiting these neurons, we also determined that KOR neurons in the medulla are required for stress-induced analgesia.

Conclusions: These discoveries highlight a distinct population of medullary neurons that broadly and robustly inhibit itch as well as acute and chronic pain in mice.

Significance: These approaches that make use of the powerful endogenous pain-modulatory system can reduce the need for pharmacological treatments, such as opioids, with fewer side effects and improved outcomes for the treatment of pain disorders.

Research/grant support: Virginia Kaufman Endowment Fund, NIH/NIAMS grant AR063772, NIH/NINDS grant NS096705 (PI: Sarah Ross), NRSA F31 grant F31NS113371 (PI: Eileen Nguyen).

Abstract 4

CONTRIBUTION OF PERIPHERAL SENSITIZATION TO CENTRAL NEUROPATHIC PAIN IN A MOUSE MODEL OF MULTIPLE SCLEROSIS

Nguyen KL,[1] Taylor BK[1]

[1]Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh School of Medicine

Introduction: Over 50% of patients with multiple sclerosis (MS) suffer from neuropathic pain (MSNP), however, current treatments provide inadequate relief. This is largely due to lack of knowledge regarding underlying mechanisms. In a widely used animal model of MS, experimental autoimmune encephalomyelitis (EAE), recent electrophysiological recordings of primary afferent neurons (PAN) in the dorsal root ganglion revealed: 1) hyperexcitability of medium-to-large diameter neurons and 2) an increase in afterhyperpolarization of small-diameter fibers. These data provide the premise for our long-term goal to understand the contribution of unmyelinated nonpeptidergic and large diameter Aß PANs to MSNP.

Methods: To evaluate the contribution of peptidergic or non-peptidergic neurons to the maintenance of MSNP, we intrathecally administered capsaicin or IB4-saporin, respectively, two weeks following the induction of EAE.

Results: We found that IB4-saporin, but not capsaicin, partially reduced mechanical hypersensitivity (plantar application of von Frey hairs to the hindpaw) and cold hypersensitivity (plantar application of a drop of evaporative acetone).

Conclusions: These data suggest that nonpeptidergic C-fibers contribute to MSNP.

Significance: Our next studies will use chemogenetics and optogenetics to modulate the activity of genetically-identified subsets of nonpeptidergic C-fibers (using $Mrgprd^{CreER}$ mice) and large diameter A-b fibers (using $TrkC^{CreER}$ mice).

Research/Grant Support: T32GM075770 (PI: Yan Xu, PhD), NIHR01DA037621 (PI: Bradley K. Taylor, PhD), R01NS112632 (PIs: Bradley K. Taylor, PhD & Patrick Sheets, PhD), R01NS062306 (PI: Bradley K. Taylor, PhD)

Abstract 5

ACTIVATION OF KAPPA OPIOID RECEPTOR-EXPRESSING NEURONS IN THE VENTRAL TEGMENTAL AREA ATTENUATES OPIOID WITHDRAWAL

Holland R,[1,2] Chiang M,[1,2] Ross S[1,2,3]

[1]Pittsburgh Center for Pain Research, University of Pittsburgh School of Medicine
[2]Department of Neurobiology, University of Pittsburgh School of Medicine
[3]Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh School of Medicine

Introduction: Opioid withdrawal is an excruciating and potentially life-threatening syndrome resulting from abrupt cessation of opioid use. Untreated opioid withdrawal frequently results in relapse and presents a major barrier to recovery from opioid use disorder (OUD). The kappa opioid receptor (KOR) has been shown to play complex roles in chronic pain and addiction through the modulation of dopamine neurons originating from the ventral tegmental area (VTA). However, the precise mechanisms through which KOR-expressing VTA (KOR^{VTA}) neurons contribute to the development of opioid withdrawal remains elusive.

Hypothesis: KOR^{VTA} neurons attenuate opioid withdrawal.

Methods: RNAScope fluorescence *in situ* hybridization (FISH) was first performed in C57BL/6J mice to genotype neurons in the VTA which express KOR. The *Oprk1*^{cre} mouse was then utilized alongside cre-dependent viral approaches to genetically manipulate KOR^{VTA} neurons in morphine-naïve and dependent mice. Withdrawal was induced by administering escalating doses of morphine followed by naloxone; acute withdrawal behaviors, real-time place preference (RTPP), and conditioned place aversion (CPA) were assessed.

Results: KOR is expressed in the vast majority of dopaminergic VTA neurons including those which co-express glutamate, whereas it is seldom expressed in solely glutamatergic or GABAergic neurons. In morphine-naïve mice, chemogenetic activation of KOR^{VTA} neurons increased sensory withdrawal thresholds and induced hyperlocomotion. In morphine-dependent mice, chemogenetic activation of KOR^{VTA} neurons reduced naloxone-precipitated withdrawal behaviors and abolished naloxone-precipitated morphine withdrawal-induced CPA. Interestingly, while optogenetic activation of these neurons did not induce a RTPP in morphine-naïve mice, morphine-dependent mice expressing channelrhodopsin (ChR2) in KOR^{VTA} neurons spent more time in the light-paired chamber than controls.

Conclusions: KOR marks a large subset of dopamine neurons in the VTA. In morphine-naïve mice, activation of KOR^{VTA} neurons modulates acute pain and locomotion. In morphine withdrawal, activation of KOR^{VTA} neurons attenuates behavioral measures of withdrawal.

Significance: This study uses cutting-edge genetic approaches to demonstrate, for the first time, the effect of selective activation of KOR neurons in the VTA on opioid withdrawal in rodents. Taken together, this evidence strongly implicates KOR-mediated downregulation of VTA neurons in aversive states and identifies potential therapeutic targets in the treatment of opioid withdrawal.

Research/Grant Support: NINDS R01NS096705 (PI: Sarah E. Ross, PhD) NINDS F31NS116981 (PI: Ruby A. Holland)

Abstract 6

ETHANOL INDUCES ALTERATIONS IN THE NON-CODING TRANSCRIPTOME OF MICROGLIAL CELLS

Rathod R,[1] Baratta A,[2] Ferguson C,[1] Homanics G,[1,2,3,4] Farris S[1,5]*

[1]Department of Anesthesiology & Perioperative Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA USA
[2]Center for Neuroscience, University of Pittsburgh School of Medicine, Pittsburgh, PA USA
[3]Department of Pharmacology & Chemical Biology, University of Pittsburgh School of Medicine, Pittsburgh, PA USA
[4]Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, PA USA
[5]Department of Biomedical Informatics, University of Pittsburgh School of Medicine, Pittsburgh, PA USA

Introduction: Alcohol Use Disorder (AUD) is a highly prevalent comorbid psychiatric disorder affecting millions of individuals throughout the world. Both human and animal studies have suggested a number of molecular mechanisms involved in the development of AUD; however, many of the underlying systems involved in the etiology of this disorder are still unknown. Dysregulation of neuroimmune and epigenetic intracellular signaling pathways are two biological systems known to be affected by excessive alcohol consumption. While less than 2% of the mammalian genome encodes for proteins, a substantial fraction of the genome is transcribed as non-coding RNA (ncRNA). Although emerging evidence suggests a critical role for ncRNAs in the neuropathology of AUD, the functional involvement of ncRNAs in AUD and neuroimmune pathways remains largely unexplored.

Hypothesis: ncRNAs are key regulators of protein-coding genes, and signaling pathways, involved in the neuroimmune system.

Methods: To determine the potential interactive role of ncRNAs in AUD and the neuroimmune system we cultured primary microglia (the resident neuroimmune cells of the brain) from male and female C57BL/6J mice and treated with or without 50mM (~200 mg/dL) ethanol. Total RNA was isolated and used for microarray analysis.

Results: Genome-wide profiling of messenger RNA (mRNA), long non-coding RNA (lncRNA), microRNA (miRNA), and circular RNA (circRNA) from microglia exposed to 50 mM of ethanol demonstrated a larger number of ncRNAs are dysregulated compared to protein-coding genes.

Conclusion: Our findings suggest that EtOH induced alterations in the expression of ncRNAs of microglial cells and potentially involved in the regulation of neuroimmune pathways.

Significance: Overall, our work will provide new mechanistic insights into ethanol-induced alterations of microglia and potentially contribute to the rationale design of novel pharmacotherapies for AUD.

Research/Grant Support: NIAAA U01-AA020889 (PI: Gregg E Homanics, PhD), R00-AA024836 (PI: Sean P. Farris, PhD)

BREAKOUT ROOM 2

Department of Anesthesiology and Perioperative Medicine

Clinical/Health Services

Moderators **Sherry Chou, MD**

Dennis Simon, MD

Abstract #	**Presenter**
7	Andrea Ibarra, MD
8	Daniella Ohnemus, MD
9	Nathan Reinert
10	Anne Wanaselja, MD (1)
11	Anne Wanaselja, MD (2)
12	David Wang, MD

Abstract 7

THE IMPACT OF SOCIOECONOMIC STATUS IN PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICES (LVADS)

Ibarra A,[1] Howard-Quijano K,[1] Hickey G,[3,4] Chen S,[3] Thoma F,[3] Mahajan A,[1] Kilic A[2,4]

[1]Division of Anesthesiology and Perioperative Medicine, University of Pittsburgh School of Medicine
[2]Division of Cardiac Surgery, University of Pittsburgh Medical Center
[3]Heart and Vascular Institute, University of Pittsburgh Medical Center
[4]Division of Cardiology, University of Pittsburgh Medical Center

Introduction: About 2500 new LVAD implants occur annually in the US[1] providing heart failure (HF) patients with improved functional capacity and quality of life.[2] Evolving LVADs have steadily showed improved survival[3] however, post-implantation hospital readmission rate still remains high ranging from 31-82%.[4–6] Socioeconomic status (SES) is a powerful predictor of adverse outcomes among HF patients[7] but its impact on survival and readmission following LVAD implantation is poorly understood.

Hypothesis: We hypothesized that patients from the most disadvantaged group (highest area deprivation index (ADI) will have increased risk of death and readmission after receiving LVAD implantation.

Methods: This is a retrospective study from a single institution evaluating patients who received LVAD implantation (Heartmate III and Heartware HVAD) between 2009-2018. Baseline characteristics were obtained from all the participants. SES indicators included ADI, race, and income. Mortality was considered as an event occurring between the LVAD implantation and October 2020 whereas readmission as the first event after discharge from LVAD implantation.

Results: We evaluated 191 patients and compared their baseline characteristics by ADI quartiles, race, and income. In comparison to the most disadvantaged group, the least disadvantaged was older (65 vs 57, $p<0.01$). African Americans lived in more deprived neighborhoods than whites (ADI 87 vs 62, $p<0.001$). Patients with high income had higher preoperative BUN and creatinine and lower preoperative albumin levels ($p=0.04$, 0.01, 0.03, respectively) than those from low income. The most disadvantaged group had a decreased risk of death in comparison to the least disadvantage one, however this was no longer significant after adjusting for age, LVAD indication and INTERMACS profile. No difference in risk of readmission was observed based on ADI. There was no difference in overall survival and readmission based on race or income.

Conclusion: Although there are differences in patient characteristics by SES indicators, these factors are not independent predictors of mortality and readmission after LVAD implantation.

Significance: When evaluating patients for LVAD implantation, SES should not be considered an absolute risk factor for adverse outcomes as preoperative comorbidities may be a larger risk factor. More studies are needed to evaluate individual SES affecting these outcomes.

Research/Grant Support: This research was supported in part by a grant from the National Institutes of Health (T32GM075770).

Abstract 8

PERIOPERATIVE METABOLIC CONTROL IN PEDIATRIC PATIENTS UNDERGOING LIVER OR LIVER-KIDNEY TRANSPLANTATION FOR PROPIONIC ACIDEMIA (PA) AND METHYLMALONIC ACIDEMIA (MA)

Ohnemus D,[1] Ligocki M,[1] Vidri R,[1] Soltys K,[2] Damian D[3]

[1]UPMC Medical Education, Department of Anesthesiology and Perioperative Medicine
[2]UPMC Children's Hospital of Pittsburgh, Pediatric Transplant Surgery
[3]UPMC Children's Hospital of Pittsburgh, Department of Anesthesiology and Perioperative Medicine

Introduction: Propionic acidemia (PA) and methylmalonic acidemia (MMA) are among the most prevalent organic acidemias. The disease course is often punctuated by frequent metabolic crises and can progress to seizures, stroke, developmental delay, and death if not promptly treated. Patients with MMA also frequently develop end-stage kidney disease. Liver transplantation (LT) has recently been introduced as a strategy for bulk enzyme replacement and is sometimes combined with kidney transplantation for those with coexisting renal disease. While only providing partial enzymatic replacement, LT offers reduction in disease-related complications and increased life expectancy and quality of life (1,2). Nutritional support plays a crucial role in metabolic stabilization during the perioperative period (3). However, as PA and MMA are relatively rare, no standards for intraoperative metabolic control have been established.

Hypothesis: Metabolic control during prolonged transplant procedures in organic acidemia patients is challenging and variable.

Methods: Review of all available electronic medical records of 15 patients who underwent liver or liver-kidney transplantation for PA or MMA at the UPMC Children's Hospital of Pittsburgh between 2013 and 2020. Data points were divided into preoperative, intraoperative, and postoperative categories.

Results: Over one-third of patients received deceased donor transplants (n=10). All living-donor recipients (n=5) were admitted to the regular transplant floor the day before the transplant procedure. Six hours prior to the transplant procedure, patients were made NPO and started on a dextrose-containing solution at a glucose infusion rate (GIR) of 8-10 mg/kg/min. Median preoperative blood glucose was 93 (IQR 86-119). Intraoperatively, three patients received fat emulsion infusion and five received carnitine infusion. Postoperatively, all patients were transferred to the intensive care unit (ICU) intubated. Blood glucose tended to increase from the preoperative to the postoperative period with median preoperative blood glucose of 93 mg/dL (IQR 86-119 mg/dL) and median maximum blood glucose on postop day one (POD1) of 324 mg/dL (IQR 307-372 mg/dL). Mean lowest pH on POD1 was 7.27 (SD 0.06), and mean highest lactate was 6.4 mmol/L (SD 2.4 mmol/L). Median length of ICU stay was 10 days. No patients required readmission within the next 30 days, and no patients died during the study period. Over half (8/15) of patients experienced at least one episode of rejection but none required re-transplantation.

Conclusions: Perioperative metabolic control in this patient population remains challenging. Patients are medically fragile, transplantation necessitates a prolonged operation, and metabolic control requires continual adjustments of glucose and insulin infusions. Patients tend to emerge in the postoperative period with metabolic derangements such as increased blood glucose and lactate despite current management.

Significance: Liver and kidney transplantation can significantly improve quality of life and life expectancy in patients with PA and MMA. Outcomes depend on strict metabolic control, yet standards for management have not been established. This study is among the first to summarize perioperative metabolic control in these patients.

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3) Nizon M, Ottolenghi C, Valayannopoulos V, Arnoux JB, Barbier V, Habarou F, et al. Long-term neurological outcome of a cohort of 80 patients with classical organic acidurias. *Orphanet J Rare Dis 2013*;8:148, U.S. National Library of Medicine, pubmed.ncbi.nlm.nih.gov/24059531/.

Abstract 9

CAUSE-SPECIFIC MORTALITY AS A SEQUELA OF PERIOPERATIVE STROKE FOLLOWING CARDIAC AND VASCULAR SURGERY

Reinert N,[1,2] Patel B,[1,2] Shaer Q MD,[3] Wu L,[4] Wisniewski S,[4] Hager E,[5] Dyer M,[5] Thirumala P[1,2]

[1]University of Pittsburgh Department of Neurology, [2]University of Pittsburgh Department of Neurosurgery, [3]Emory University Department of Neurology, [4]University of Pittsburgh Department of Biostatistics, [5]University of Pittsburgh Department of Vascular Surgery

Introduction: Perioperative strokes are defined as cerebrovascular events that occur during or within 30 days of a surgical procedure. As the number of cardiac and vascular surgical interventions continues to rise globally, the burden of these perioperative strokes on morbidity and mortality will likely increase in parallel. While much is known about the risk factors for perioperative stroke, there is a paucity of data surrounding subsequent cause-specific mortality. In this study, we aim to establish the risk of cause-specific mortality associated with perioperative stroke following cardiac and vascular procedures at 30 days, 90 days, and 1-year post-op.

Hypothesis: Perioperative stroke following cardiac and vascular procedures increases the risk of cause-specific mortality from the following etiologies: cerebrovascular, cardiovascular, pulmonary, malignancy, infectious, and dementia.

Methods: This is a retrospective, observational, cohort study evaluating 277,654 cardiac and vascular surgical patients dually documented within the Inpatient Discharge Claims Database and the Pennsylvania Department of Health Death Statistics database. A univariate analysis followed by a multivariate logistic regression analysis was performed to determine the odds of cerebrovascular, cardiovascular, pulmonary, malignancy, infectious, and dementia causes of mortality following perioperative stroke.

Results: Perioperative stroke significantly increased the odds of all-cause mortality ($p<.0001$) as well as cause-specific mortalities in all categories ($p<0.05$) except dementia ($p=0.89$) at all assessed time points. The odds of cerebrovascular-related mortality were highest following perioperative stroke at 30 days post-op (aOR 34.5 [29.1, 40.9], $p<0.0001$). The association of perioperative stroke with cause-specific mortality was more pronounced at the 30-day endpoint when compared to both 90-day and 1-year mortality.

Conclusions: Perioperative stroke in the cardiac and vascular surgical population was associated with increased odds of cerebrovascular, cardiovascular, pulmonary, malignancy, infectious, and all-cause mortality at 30 days, 90 days, and 1-year post-op when compared to patients who did not suffer a perioperative stroke.

Significance: This cause-specific mortality data can inform and enhance perioperative medical management and risk stratification of patients at risk of suffering from a perioperative stroke.

Research/Grant Support: Statistical Support: NIH Grant Number - UL1TR001857.

Abstract 10

CORRELATING PRENATAL AND DELIVERY PLATELET COUNT VALUES IN OBSTETRIC PATIENTS: CLINICAL UTILITY OF REFLEXIVE ADMISSION LABORATORY ASSESSMENTS

Wanaselja A,[1] Binstock A,[2] Larkin J,[2] Lim G[1,2]

[1] Department of Anesthesiology & Perioperative Medicine, University of Pittsburgh Medical Center, University of Pittsburgh School of Medicine

[2] Department of Obstetrics, Gynecology & Reproductive Sciences, University of Pittsburgh School of Medicine

Introduction: Current practice guidelines state that admission intrapartum platelet count is not necessary in healthy pregnant patients prior to neuraxial analgesia or anesthesia [1], a test frequently ordered to identify those at risk for postpartum hemorrhage [2]. However, these recommendations are based on expert opinion and Level B2-4 evidence: non-comparative observational studies and case reports. The purpose of this study was to provide high-quality, comparative evidence to evaluate the recommendations on intrapartum laboratory testing in healthy pregnant patients.

Hypothesis: In uncomplicated pregnant patients, no difference exists between third trimester prenatal and admission intrapartum platelet count values.

Methods: Data from a single large volume tertiary care center were abstracted from medical records from January 2018 to October 2019. At this institution, complete blood counts are reflexively ordered and resulted on all women admitted for childbirth for the primary purpose of hemorrhage risk stratification. An abnormal medical history was defined as presence of one or more of the following: chorioamnionitis, hypertensive disorder, abruption or acute bleeding of any nature, placenta accreta spectrum, placenta previa, obesity (body mass index >35), 6 or more prior vaginal deliveries, and prior cesarean delivery or uterine scar. Linear and logistic regression assessed relationship between prenatal and delivery platelet counts and risk for thrombocytopenia at delivery (defined as platelet count less than 70k) after adjusting for abnormal medical history.

Results: 8,803 deliveries occurred in the study period and had both prenatal and delivery platelet counts recorded. 5,143 cases had complete labor and delivery medical history data; 1,385 (26.9%) had normal history and 3,758 (73.1%) abnormal. Prenatal platelet count was predictive of delivery platelet count (R^2 = 0.67, β=0.79, 95%CI 0.78 to 0.80, $P < 0.001$). After adjusting for abnormal history, prenatal thrombocytopenia was significantly more likely to have delivery thrombocytopenia (aOR 1714.7, 95% CI 456.6-6439.2, P<0.001). When delivery platelet counts were below 70 and prenatal counts were normal (3 outlier cases), these were instances where delivery clinical circumstances justified updated laboratory analysis.

Conclusion: Prenatal platelet count is predictive of delivery platelet count values. Further analyses can reveal the potential utility of admission hemoglobin for anemia detection, to inform obstetric hemorrhage/transfusion risk stratification.

Significance: These data provide additional evidence to support published recommendations that delivery platelet counts are not required prior to neuraxial procedures, provided that prenatal labs, patient history, and delivery circumstances are normal.

1 Practice Guidelines. Anesthesiology 2016; 124:270

2 Simon L. Br J Anaesth 1997; 78:678

Abstract 11

PATIENT PERSPECTIVES ON COMPLEMENTARY AND ALTERNATIVE MEDICINE FOR PERIPARTUM PAIN MANAGEMENT

Wanaselja A,[1] Nicholas A,[2] Larkin J,[2] Krans E,[2] Lim G[1,2]

[1] Department of Anesthesiology & Perioperative Medicine, University of Pittsburgh Medical Center, University of Pittsburgh School of Medicine

[2] Department of Obstetrics, Gynecology & Reproductive Sciences, University of Pittsburgh School of Medicine

Introduction: Satisfaction with labor analgesia is driven by the fulfillment of individual birth expectations, more so than pain intensity score reduction [1]. Complementary and alternative medicine (CAM) is associated with a sense of personal autonomy, control, and compatibility with a patient's beliefs regarding their healthcare [2]. CAM is therefore potentially a patient-centered and value-added service to hospital-based birth centers. We surveyed peripartum women to assess their interest in CAM options for pain management during and after birth.

Methods: A cross-sectional single-center survey design was chosen. A needs assessment survey was distributed to obstetric patients in the labor and delivery suite before labor, and in the postpartum unit during postpartum days 1-2. Patients were asked to rate their interest in learning about aromatherapy, biofeedback, transcutaneous electric nerve stimulation (TENS), and sterile water injections (SWI) for pain management. Questions were graded on a 1-5 scale where 1 is completely disagree and 5 is completely agree to the questions, "I am interested in learning more about X pain management techniques." Patients were also asked to select areas of interest in specific mind/body and movement/touch interventions. Descriptive statistics and box plots compared response distributions between groups. Fisher exact test compared ratings between groups.

Results: 20 surveys were distributed, and 18 women responded (90% response rate). 8 (44%) of responses were from labor and 10 (55%) were from postpartum. Both labor and postpartum groups rated interest in CAM interventions variably. Women being admitted for labor and delivery were more interested in CAM techniques than women with acute postpartum pain. Interest in TENS for pain management was significantly higher in the labor group (P=0.003). Interest in mind/body and movement/touch interventions were variable between individuals, but group patterns were apparent in favor of movement/touch in the postpartum period and both movement/touch and mind/body interventions during labor.

Conclusion: In this needs assessment, peripartum women appear consistently interested in CAM for pain management, and both labor and postpartum women express variable interest in CAM techniques. Future efforts can focus on biofeedback, TENS, massage, breathing, yoga, meditation, and mindfulness interventions in appropriate patients.

Significance: Anesthesiologists can work with hospital teams to create value for both patients and health systems, by increasing the provision of these patient-centered services during and after birth.

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2 Astin. JAMA. 1998; 279:1548

Abstract 12

EFFECT OF ISOFLURANE AND SEVOFLURANE ON MYOCARDIAL DEFORMATION: A DOSE-RESPONSE CROSSOVER STUDY

Wang DW,[1] Subramaniam K,[1] Abuelkasem E[1]

[1]Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh School of Medicine

Introduction: Volatile anesthetics can cause decreases in myocardial function. Transesophageal echocardiography (TEE) can be used intraoperatively to monitor cardiac activity, particularly in cardiac surgeries. Left ventricular ejection fraction (LVEF) remains the most common measurement of systolic function. However, myocardial deformation imaging, also known as strain imaging, may offer a more accurate depiction of cardiac function. Here, we compared the dose-dependent effects of isoflurane and sevoflurane on myocardial strain during coronary artery bypass graft surgery with speckle tracking echocardiography.

Hypothesis: Volatile anesthetics, regardless of the agent, will cause dose-dependent decreases in myocardial function, as measured by myocardial strain. In addition, sevoflurane will have more myocardial suppressant activity compared to isoflurane at equivalent anesthetic concentrations.

Methods: Twenty patients with preoperative LVEF > 50% undergoing coronary artery bypass graft surgeries were enrolled. After induction of anesthesia, TEE images were acquired sequentially at end-tidal 0.5, 1.0, and 1.5 age-adjusted minimum alveolar concentration (MAC) of sevoflurane. The volatile anesthetic agent was then switched to isoflurane, and TEE images were acquired sequentially at 0.5, 1.0, and 1.5 MAC of isoflurane. All images were recorded and analyzed offline. Left ventricular global longitudinal strain (GLS), commonly used in evaluation of cardiac strain, was determined using speckle tracking. LVEF was also calculated using the biplane Simpson method.

Results: Neither isoflurane nor sevoflurane had dose-dependent effects on myocardial strain. The direct comparison of isoflurane to sevoflurane was calculated by the ratio of isoflurane GLS to sevoflurane GLS. The isoflurane to sevoflurane GLS ratio was greater than one at each MAC level: 1.13 (95% confidence interval [CI], 1.02-1.24) at 0.5 MAC; 1.19 (95% CI, 0.98-1.41) at 1.0 MAC; and 1.17 (95% CI, 1.09-1.24) at 1.5 MAC. This finding was also observed, but diminished, in the LVEF ratio: 1.04 (95% CI, 0.98-1.09) at 0.5 MAC; 1.06 (95% CI, 0.98-1.13) at 1.0 MAC; and 1.11 (95% CI, 1.04-1.18) at 1.5 MAC.

Conclusion: Isoflurane had greater myocardial strain values compared to sevoflurane at corresponding anesthetic levels, suggesting better preservation of myocardial function. This observation was diminished when using traditional ejection fraction, possibly indicating that myocardial strain is more sensitive in detecting differences in cardiac function.

Significance: This study shows a potential benefit of isoflurane compared to sevoflurane in patients with known coronary artery disease and preserved LVEF. This can dramatically change practice in providing anesthesia, including in non-cardiac surgeries, but future research must be conducted to examine postoperative outcomes after isoflurane and sevoflurane anesthesia.

BREAKOUT ROOM 3

Department of Critical Care Medicine

Moderators **Mioara Manole, MD**

Amy Wagner, MD

Abstract #	Presenter
13	Jonathan Birabaharan, BS
14	Jeremy Herrmann, MD
15	Carlos Luis Manrique-Caballero, MD
16	Brittany Paige Nelson, MS
17	Oluwasinmisola Opeyemi, BS
18	Charith Ratnayake, BS
19	Aditya Datt Sharma
20	Kara Snyder, BS

Abstract 13

A SENSITIVE, HIGH-THROUGHPUT UPLC-MS/MS PANEL ASSAY TO MEASURE PLASMA CONCENTRATIONS OF SEDATIVES AND THEIR METABOLITES IN CRITICALLY ILL CHILDREN

Birabaharan J,[1] West R,[2] Nolin TD,[2] Empey PE[2]

[1]Departments of Pharmaceutical Sciences and [2]Pharmacy & Therapeutics, Center for Clinical Pharmaceutical Sciences, University of Pittsburgh School of Pharmacy

Introduction: Increased sedative exposure is a known delirium risk factor in critically ill children. Reduced drug clearance may predict occurrence and severity. We are conducting a multicenter clinical trial using population pharmacokinetic modeling of drug concentrations as a novel approach to these determine dose-concentration relationships. However, limited plasma volume is available and multiple assays are required to quantify midazolam (MDZ), dexmedetomidine(DEX), morphine(MOR), hydromorphone(HM), and fentanyl(FEN), and their metabolites, limiting feasibility.

Hypothesis: Sensitive and specific simultaneous quantification of MDZ, 1-OH MDZ, DEX, MOR, MOR3G, MOR3G, FEN, norfentanyl, and HM in small volume pediatric samples is feasible.

Methods: Ultra Performance liquid chromatography method with tandem mass spectrometry (UPLC-MS/MS) was developed. Analyte separation was achieved using a gradient mixture of (A: 0.15% formic acid in water and B: Acetonitrile) and a Waters Acquity C18, 1.7um (2.1 x 100mm) column. A simple protein precipitation extraction using acetonitrile was utilized to remove biological matrix. Analytes were detected using heated electrospray ionization and selected reaction monitoring (Thermo Fisher Scientific TSQ Quantum).

Results: Assays were linear over the expected clinical concentration ranges: MDZ, MOR, HM: 0.5-125ng/mL; 1-OH MDZ, MOR3G, MOR6G: 5-500ng/mL; and DEX, FEN, norfentanyl: 0.05-7.5ng/mL (R^2=0.99 for all). Lower limits of quantification were 0.5 ng/mL, 5 ng/mL and 0.05 ng/mL, respectively. Assay run time was 10 min and only required 100 uL of plasma.

Significance: We developed a novel method to measure multiple sedatives and their metabolites simultaneously. This panel is the most comprehensive sedative assay available. It is also efficient, sensitive, and specific; requiring minimal plasma volume that is available in pediatric patients. It enables sedative population PK modeling to understand altered pharmacokinetics and delirium relationships such as in the concurrent multicenter trial of pediatric ICU patients.

Research/Grant Support: NICHD 1R01HD099284-01(PI: Empey/ Bell/Traube). NIH TL1 TR001858 (PI: Kraemer, Kevin)

Abstract 14

DIVERGENT EFFECTS OF THERAPEUTIC HYPOTHERMIA ON COLD STRESS HORMONES AFTER PEDIATRIC CARDIAC ARREST

Herrmann J,[1,3] Fink E,[1,2,3] Fabio A,[4] Au A,[1,2,3] Berger R,[2,3] Janesko-Feldman K,[1,3] Clark RSB,[1,2,3] Kochanek PM,[1,2,3] Jackson T[5]

[1]Departments of Critical Care Medicine and [2]Pediatrics, [3]Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine and UPMC Children's Hospital of Pittsburgh, and the [4]Graduate School of Public Health, University of Pittsburgh, Pittsburgh, PA

[5]Department of Molecular Pharmacology and Physiology, University of South Florida Morsani College of Medicine, Tampa, FL

Introduction: Cold-stressors stimulate production of cold stress hormones (CSHs) which promote thermogenesis and may be neuroprotective. Studies of cold exposure and CSH levels in humans assessed healthy patients; it is unclear if cooling critically ill patients increases circulating CSHs. Fibroblast Growth Factor-21 (FGF21) and Growth Differentiation Factor-15 (GDF-15) are putative neuroprotective CSHs upregulated by cold exposure and other stimuli. However, both proteins associate with poor outcome in adult cardiac arrest (CA), which may reflect insult severity rather than neurotoxicity. β-klotho is the target engagement co-receptor for FGF21; β-klotho levels are abundant in the infant brain, decrease with age, and are low-to-absent in adults. GDNF-family receptor α-like (GFRAL) is the target engagement receptor for GDF-15; GFRAL is absent in most brain regions across all ages. Together this suggests the possibility that therapeutic hypothermia (TH) may preferentially promote FGF21-mediated neuroprotective mechanisms in children.

Hypothesis: CSHs are increased in the pediatric CA population and are augmented by TH.

Methods: We performed a secondary analysis of serum samples collected in clinical trials and measured FGF21 and GDF-15 levels (ELISA) in pediatric patients post-CA. We compared post CA levels to healthy controls and children admitted to the PICU for non-neurologic causes. Post-CA, we compared normothermia (NT) vs TH (33°C for 72h) treated cohorts at <24h, 24h, 48h, 72h, 96h. We also explored the association between hospital mortality and <24h levels and tested the hypothesis that CSHs increase at 72h in TH vs NT.

Results: We assessed 164 samples from 68 patients (27 CA [14 TH, 13 normothermia], 9 PICU and 32 healthy controls). Median initial FGF21 and GDF-15 levels were higher in the post-CA group (392pg/mL, 7,089pg/mL, respectively) vs. healthy controls (40pg/mL, 396pg/mL) ($P<0.001$, $P=0.0001$ between all groups). Hospital mortality was associated with higher initial GDF-15 post-CA (19,450pg/mL vs 5,337pg/mL, $P<0.05$), but not FGF21 (757pg/mL vs. 248pg/mL, $P=0.200$). At 72h, the median change in FGF21 vs. baseline was higher in TH (231pg/mL) vs. normothermia (–20pg/mL) ($P<0.05$), with no difference in GDF-15 (-2,816pg/mL vs. -1,867pg/mL, $P=0.973$).

Conclusion: FGF21 and GDF-15 increased after pediatric CA, but only FGF21 responded to TH.

Significance: FGF21 signaling may contribute to hypothermia induced neuroprotection in children. Comprehensive investigation of CSHs post-CA, impact of age, response to TH, and neuroprotection is warranted.

Grant Support: Lloyd Reback Family Gift Award

Abstract 15

MICROCIRCULATORY DYSFUNCTION IN SEPSIS-ASSOCIATED ACUTE KIDNEY INJURY IS NOT EQUIVALENT TO IMPAIRED TISSUE OXYGENATION

Manrique-Caballero C,[1] Toro J,[1] Baty C,[2] Oberbarnscheidt M,[3] Del Rio-Pertuz G,[1,4] Aleem S,[5] Frank A,[1] Lakkis F,[3] Zuckerbraun B,[3] Pinsky M,[1] Vinogradov S,[6] Kellum J,[1] Gomez H[1,7]

[1]Center for Critical Care Nephrology, Department of Critical Care Medicine, University of Pittsburgh [2]Renal Electrolyte Division – Department of Medicine, University of Pittsburgh, [3]Department of Surgery, [4]Department of Internal Medicine, Texas Tech University Health Sciences Center, [5]Department of Pulmonary and Critical Care Medicine, Virginia Tech Carilion Clinic [6]Department of Chemistry, University of Pennsylvania, [7]Vascular Medicine Institute of the University of Pittsburgh.

Background: Sepsis is a common and frequently fatal condition in which mortality is associated with organ dysfunction. However, the mechanisms by which sepsis causes organ dysfunction are not well understood. Microcirculatory dysfunction has been proposed as one of the mechanisms by which sepsis causes acute kidney injury (AKI). However, it remains unclear whether microcirculatory dysfunction causes injury through tissue hypoperfusion or increased local inflammation.

Hypothesis: Microcirculatory dysfunction in sepsis-associated AKI is not directly correlated with impaired cortical oxygenation.

Methods: C57Bl/6 mice (n=5-8 per group) were randomly assigned to cecal ligation and puncture (CLP), as a model of sepsis, or sham surgery as a control group. We measured the following outcomes at 24 hours: serum creatinine (sCr) as a marker of renal injury, IL-6 to assess systemic inflammatory response, and mortality. Tissue oxygenation in the renal cortex was measured using a novel phosphorescent probe, Oxyphor 2P. As O2 can quench the phosphorescence emitted by the Oxyphor 2P after excitation using a laser, the phosphorescence decay time is equated to the partial pressure of O2 in the tissue. Phosphorescence decay times were measured sequentially in four different locations of the kidney during one minute. Renal microcirculatory flow was assessed using 2P intravital microscopy by quantification of the microvascular flow index (MFI).

Results: Sepsis induced by CLP resulted in higher levels of renal injury biomarkers (CLP 1.66 vs Sham 0.98; $p=0.05$), systemic inflammatory markers (CLP 7759.28 vs Sham 79.1; $p<0.001$), microcirculatory dysfunction evidenced by an MFI < 2.6 (CLP 2.33 vs Sham 2.67; $p=0.38$), and higher mortality at 24 hours (CLP 46.8% vs Sham 100%; $p<0.01$), as compared to sham surgery. However, renal cortex oxygenation was increased in animals exposed to CLP as compared to sham (CLP 53.7 vs Sham 41.2; $p<0.001$).

Conclusions: Microcirculatory dysfunction during sepsis is not associated with impaired cortical tissue oxygenation during experimental sepsis. These findings suggest that there may be mechanisms other than hypoxia by which microvascular dysfunction can cause TEC injury.

Significance: This project proposes a novel mechanism of injury in sepsis-AKI in which decrease oxygenation to tissues is not the main driver of damage suggesting that other mechanisms either metabolic or inflamamtory must be at play.

Grant Support: Hernando Gomez: VMI P3HVB Program, 1K12HL109068-02 and 1K08GM117310-01A1

Abstract 16

NOVEL MANGANESE METALLOPORPHYRIN IMPROVES SPATIAL MEMORY ACQUISITION AFTER CONTROLLED CORTICAL IMPACT

Nelson BP,[1] Piganelli JD,[3,4] Vagni V,[1] Clark RS,[1,2,5,6] Bayır H,[1,2,5,6] Simon DW[1,2,5,6]

[1]Safar Center for Resuscitation Research, [2]Children's Neuroscience Institute, Departments of [3]Surgery, [4]Immunology, [5]Critical Care Medicine, and [6]Pediatrics
University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Introduction: Oxidative stress after traumatic brain injury (TBI) may overwhelm antioxidant defenses such as superoxide dismutase (SOD) and antioxidants leading to secondary brain injury. The manganese metalloporphyrin MnTnBuOE-2-PyP^{5+} (BMX-001) was developed as a SOD-mimic with increased lipophilicity to cross the blood brain barrier and reduced toxicity relative to other SOD mimics. BMX-001 is being investigated in Phase II and Phase III trials for radioprotection in cancer treatment but has not been evaluated in TBI.

Hypothesis: We hypothesized that BMX-001 will improve spatial memory acquisition and reduce lesion volume after controlled cortical impact (CCI).

Methods: Adult male C57BL6/J mice were randomly assigned to one of four groups (n=10/group): Sham+vehicle, Sham+BMX-001, CCI+vehicle, and CCI+BMX-001. CCI was performed with a 3mm impactor tip and injury level of 6m/s, 2mm depth, and 50msec dwell. Based on previous toxicologic studies, a dosing regimen of 12mg/kg SQ given 10min after CCI followed by an infusion of 3mg/kg/day delivered SQ via Alzet pump was selected. Morris water maze (MWM) was performed on days 14-19 after injury. Mice were sacrificed after completion of behavioral testing and lesion volume assessed. Data was analyzed by student *t* test or RM 2-way ANOVA with Bonferroni's adjustment for multiple comparisons.

Results: Overall, CCI+BMX-001 mice had significantly reduced latency to find the hidden platform relative to CCI+vehicle ($p<0.01$). Analysis of individual days found that CCI+BMX-001 mice had reduced latency to find the hidden platform on days 15 and 16 after injury compared to CCI+vehicle ($p<0.0001$). No difference was observed between Sham+vehicle and Sham+BMX-001. Lesion volume was 22.2 ± 1.0 mm^3 and 23 ± 1.0 mm^3 in vehicle and BMX-001 treated mice respectively ($p=0.6$). Hemispheric volume loss was $29.9 \pm 0.7\%$ and $28.6 \pm 1.3\%$ in vehicle and BMX-001 treated mice respectively ($p=0.4$).

Conclusions: BMX-001 improved spatial memory acquisition after CCI. There was no difference in lesion volume between CCI+Vehicle and CCI+BMX-001 mice.

Significance: BMX-001 may represent a novel therapeutic to reduce secondary injury after TBI. Additional preclinical investigations to confirm neuroprotection and determine potential mechanisms are warranted.

Research/Grant Support: Children's Hospital of Pittsburgh RAC

Abstract 17

IS DEXMEDETOMIDINE ASSOCIATED WITH DECREASED OPIOID REQUIREMENT AMONG CRITICALLY ILL CHILDREN?

Opeyemi O,[1] Crisamore K,[2-4] Pelletier J,[2,3] Rakker J,[2,3] Au A,[2,3] Empey P,[2-4] Clark R,[2,3] Horvat C[2,3]

[1]University of Pittsburgh School of Medicine
[2]Department of Critical Care Medicine, University of Pittsburgh School of Medicine
[3]Safar Center for Resuscitation Research, University of Pittsburgh
[4]Department of Pharmacy and Therapeutics, University of Pittsburgh School of Pharmacy

Introduction: Children admitted to the pediatric intensive care unit (PICU) often require potent sedative and analgesic medications to treat pain associated with their illness. Dexmedetomidine (DEX) is a commonly used sedative that may also reduce the requirement for other sedative-analgesic medications, including opioids.

Hypothesis: We hypothesized that use of DEX among children in the PICU with respiratory failure receiving a concomitant opioid infusion would be associated with a reduced opioid dose requirement.

Methods: The study consisted of a retrospective cohort of children admitted to the PICU between 2010 and 2019 at a quaternary children's hospital. Inclusion criteria consisted of non-surgical admissions receiving mechanical ventilation with a concomitant opioid infusion for the first 72 hours of PICU admission. Multivariable linear regression was used to identify factors associated with mean opioid exposure. A propensity matched analysis examined opioid exposure after adjusting for factors associated with the receipt of dexmedetomidine in the first 24 hours of PICU admission.

Results: There were 734 encounters that met inclusion criteria, with 163 (22%) receiving a DEX infusion in the first 24 hours. Age, sex, and race had no significant difference between the early and no dexmedetomidine groups. The regression model explained 49.6% of variance in mean opioid exposure. DEX infusion initiated in the first 24 hours of PICU admission was not associated mean opioid exposure after adjusting for covariates (β=0.17, P=0.07). In the propensity matched analysis, initiation of an early DEX infusion was significantly associated with an estimated a greater mean 72-hr opioid exposure compared to patients who did not receive DEX (estimated increase of 0.01 mili-morphine-equivalent per kilogram, P=0.02).

Conclusions: Early DEX was not significantly associated with mean 72-hr opioid exposure among children admitted to the PICU with respiratory failure. A propensity-matched analysis indicated patients receiving early DEX also received more opioid, a finding that could reflect confounding by indication. More work is needed to assess the possible effects of residual confounding in this cohort.

Significance: The findings from this work can be used to inform clinical researchers of factors worth considering when designing trials assessing sedation-analgesia strategies for critically ill children with respiratory failure.

Research/Grant Support: 5K23HD099331-02 (CMH); 5T32HD040686-20 (JHP), 5K23NS104133 (AKA), 5T32HD040686-19 (JR); TL1TR001858(KC); The American Foundation for Pharmaceutical Education; Clinical Scientist Training Program Scholar Award

Abstract 18

NEUTROPHIL TO LYMPHOCYTE RATIO PREDICTS SYSTEMIC INFLAMMATION AND POOR ACUTE OUTCOME IN SUBARACHNOID HEMORRHAGE

Ratnayake C,[4] Hammond M,[2] Sharma AD,[5] Alpargu G,[7] Altamirano V,[1] Pandya Y,[3] Villamizar C,[4] Fang Yu, Molyneaux B,[1] Gross B,[3] Rao C,[6] Chou SH[1,2,3,4]

[1]Department of Critical Care Medicine, [2]Department of Neurology; [3]Department of Neurosurgery;
[4]University of Pittsburgh School of Medicine; [5]University of Pittsburgh
[6]Baylor College of Medicine; [7]California State University Fullerton

Introduction: Emerging evidence suggests systemic inflammation worsens ischemic stroke and hemorrhagic stroke outcomes. While neutrophil- to-lymphocyte ratio (NLR), a marker of systemic inflammation, may be associated with subarachnoid hemorrhage (SAH) outcome when measured on hospital admission, there is little data on how NLR over time may impact SAH outcome.

Hypothesis: We hypothesize that elevated NLR over time during acute SAH may be associated with short term outcome.

Methods: Adult patients presenting within 96 hours of spontaneous SAH admitted to a single academic center between 1/1/2017 to 1/1/2020 were included. Investigators determined time of SAH onset, SAH clinical (Hunt and Hess) and radiographic severity scores (modified Fischer), angiographic vasospasm, delayed cerebral ischemia, and functional outcome measured by modified Rankin Score (mRS) at hospital discharge. Temporal profiles of neutrophil and lymphocyte counts and NLR on post-SAH onset days 1 – 10 were compared between favorable (mRS <= 3) and unfavorable (mRS >3) outcome groups. We used linear mixed effect models with repeated measures to determine whether NLR temporal profiles were independently associated with SAH outcome and systemic inflammatory response burden (SIRS).

Results: Total cohort had 229 patients with a mean age of 59 years and 71% female. NLR from post-SAH day 0-10 is elevated patients with unfavorable outcome. Between-group difference remained statistically significant after adjusting for age and clinical severity score ($p<0.0001$). There is no interaction between outcome groups over time ($p=0.38$). Absolute neutrophil ($p=0.055$) did show a between group difference over time while lymphocyte count ($p=0.68$) did not. Finally, NLR was correlated SIRS burden throughout the entire hospital stay and did not show a between group difference ($p=.117$).

Conclusions: Elevation in peripheral blood NLR over time during acute SAH was strongly associated with unfavorable short-term outcome at hospital discharge after adjusting for age and SAH clinical severity grade effects. Future studies are needed to validate this finding and to investigate potential mechanisms action of NLR and systemic inflammation on SAH outcome.

Significance: With a more nuanced understanding of the temporal changes in SAH pathogenesis, specifically targeted treatments towards immune populations that differ temporally between outcome groups (i.e., neutrophils) may yield improved treatment.

Research Support: UL1 TR001857 (PI: Sherry Chou, MD, MMSC, FNCS)

Abstract 19

EFFECT OF THE COVID-19 PANDEMIC ON ICU ISCHEMIC AND HEMORRHAGIC STROKE OUTCOMES

Sharma A,[1] Ratnayake C,[2] Paul N,[2] Safonova A,[2] Altamirano V,[3] Skeel A,[1] Hammond M,[3] Scott A,[3] Kaplan L,[2] Venkatasubba Rao C,[6] Chou SH[2,3,4,5]

[1]University of Pittsburgh, [2]University of Pittsburgh School of Medicine, [3]Department of Critical Care Medicine, [4]Department of Neurology, [5]Department of Neurosurgery, [6]Baylor College of Medicine; Departments of Neurology, Neurosurgery and Center for Space Medicine

The aim of this study was to evaluate impact of COVID-19 pandemic on mortality and care limitations in critically-ill stroke patients

Introduction: COVID-19 pandemic overwhelmed medical systems leading to resource shortages in many regions, which may impact care limitations and mortality in non-COVID patients. This is of particular concern in severe stroke population where perceived poor prognosis can lead to early care limitations and the self-fulfilling prophecy of worse outcomes.

Hypothesis: Resource shortages inflicted by the COVID-19 pandemic may have a negative effect on the outcomes of critically ill stroke patients.

Methods: During first 3 months of COVID-19 pandemic (03/28/20-06/28/20) we prospectively enrolled consecutive adults with acute ischemic stroke (AIS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) meeting pre-pandemic criterial for intensive care unit (ICU) admission at single comprehensive stroke center, systematically recorded COVID-19 status, pre-existing code status, disease severity, transition to do-not-resuscitate (DNR), do-not-intubate (DNI), and comfort measures (CMO) code status and in-hospital mortality. Results were compared with a 3-months retrospective cohort from prior to global COVID-19 pandemic (10/1/19-12/31/19).

Results: Pandemic cohort (N=196, mean age 63, 48% female, 60% AIS, 26% ICH, 14% SAH, 22% COVID-19 person-under-investigation) and pre-pandemic cohort (N=199, mean age 63, 46% female, 58% AIS, 26% ICH, 16% SAH) were similar. Our hospital did not experience resource shortages during peak pandemic. Compared with the pandemic cohort, pre-pandemic cohort had similar stroke severity scores but more pre-existing care limitations at admission (90% vs. 98% full code, p=0.005), more frequent transition to do-not-resuscitate (13% vs. 5%, p=0.0025), Do-Not-Intubate (10% vs. 3%, p=0.0078), and higher in-hospital mortality (21% vs. 9%, p=0.0012).

Conclusion: COVID-19 pandemic was associated with lower incidence of care limitations and in-hospital mortality in severe stroke patients at a stroke center that did not experience resource shortages.

Significance: Further studies are needed to determine whether these results are due to in-person family visit restrictions during the pandemic. Multicenter studies are needed to determine whether these observations hold true in centers impacted by resource shortages.

Research/Grant support: This research is a part of the GCS-NeuroCOVID consortium OUTCOMES study.

Abstract 20

AN INVESTIGATION OF SEX-DEPENDENT DIFFERENCES IN A MURINE MODEL OF MECHANICAL STRETCH-INJURY IN PRIMARY CORTICAL NEURONS

Snyder K,[1] Gorse K,[1] Kochanek PM,[2] Jackson TC[1]

[1]University of South Florida, Morsani College of Medicine, Department of Molecular Pharmacology & Physiology, Tampa FL. [2]University of Pittsburgh, School of Medicine, Department of Critical Care Medicine, Pittsburgh PA

Introduction: Traumatic brain injury (TBI) is a leading cause of death and disability in the US. The incidence of adult TBI is higher in men, and sex-dependent differences influence secondary mediators of neuronal injury. The cell injury controller II (CICII) is a commercially available device for studying TBI-like injuries in culture. Here we studied sex-dependent differences in the magnitude of neuronal damage produced by a mechanical stretch insult to primary mouse cortical neurons grown in the next-generation cell culture medium Neurobasal™/B27-Plus.

Hypothesis: Male-enriched mouse cortical neurons will exhibit greater neuronal death vs. females, assessed using levels of lactate dehydrogenase (LDH) at 24h post-injury.

Methods: Fetal cortices were harvested from ~E15-18 C57BL/6 embryos. Male vs. female embryos were identified visually and separated. Tail snips were collected for RT-PCR analysis of sex-determining region Y (SRY) to confirm enriched male vs. female neurons. Cortical tissue was dissociated, and neurons maintained in Neurobasal™-Plus/B27-Plus. Matrigel-coated BioFlex Silastic plates, seeded with $1.5x10^6$ neurons/well, were maintained at 37°C in a 5% CO_2 incubator. On day *in vitro* 10 (DIV10) wells were given a stretch-injury (85ms burst, targeting 38%, 54%, 64%, or 75% stretch). 24h later (DIV11), media was collected for LDH analysis and neurons harvested for either Western blot or fixed for immunofluorescence. LDH levels (% cytotoxicity) were analyzed by One-Way-ANOVA (kill-curve studies) or Two-Way-ANOVA (sex vs. insult). Post-hoc analysis was performed using a Tukey test. Data were significant at $p < 0.05$.

Results: In mixed-sex cultures (n=9/group; three independent experiments), 24h LDH levels progressively increased as the insult level (peak well pressure) was increased). The averaged % cytotoxicity was 9.76±4.91 (control), 10.85±5.38 (38% stretch), 15.77±8.14 (54% stretch), 25.19±12.22 (64% stretch), and 38.01±21.98 (75% stretch). Sex-dependent vulnerabilities were studied at the 64% insult level (n=4/group). 24h LDH levels were 29.19±6.22 in injured female-enriched neurons vs. 16.49±3.90 in males. The effect of injury and sex on LDH levels was highly significant ($p<0.0001$ and $p<0.0015$, respectively), and interacted ($p=0.0449$). Post-hoc analysis confirmed that female neurons were significantly more injured vs. males ($p=0.0036$). SRY expression confirmed >90% male neurons and 100% pure female neurons.

Conclusions: Stretch-injured mouse neurons grown in Neurobasal™/B27-Plus had robust damage at the 64% and 75% insult levels. The magnitude of cell death was greater vs. that seen in our prior reports using BrainPhys™/SM1, in rat cortical neurons. This may suggest that either the use of mouse neurons and/or Neurobasal™/B27-Plus medium augments the severity of the model. Furthermore, unexpectedly, female neurons had greater vulnerability to a stretch-injury.

Significance: We have established an experimental approach to study the influence of sex-dimorphic effects on neuronal damage in an *in vitro* TBI model. Our system provides a useful framework to test if the efficacy of novel pharmacotherapies and therapeutic gene targets for TBI are further modulated by sex.

Research / Grant Support: NIH/NINDS grant R01NS105721 (PI: Travis C. Jackson, PhD)

BREAKOUT ROOM 4

Department of Emergency Medicine

Moderators **Alicia Au, MD**

Ericka Fink, MD, MS, FCCM

Abstract #	Presenter
21	David Barton, MD
22	Patrick Coppler, PA-C
23	Vignesh Gunasekaran, MBBS
24	Mark Ryan Hincapie, MD, FAAP
25	Andrew Rowley, BS, and Nicole Alindogan
26	Daniel Edwin Inks Schloss, MD
27	Kyle Schmucker, MD
28	Sofia Seppi

Abstract 21

NEUROFILAMENT PROTEINS IN SERUM AND CSF IN TWO COHORTS WITH TRAUMATIC BRAIN INJURY

Barton D,[1] Vaughan L,[2] Xu H,[3] Yang Z,[3] Trifilio E,[3] Williamson J,[3] Rubenstein R,[4] Robertson C,[5] Wagner A,[2] Wang K[3]

[1]Department of Emergency Medicine, University of Pittsburgh; [2]Department of Physical Medicine & Rehabilitation, University of Pittsburgh; [3]Departments of Psychiatry, Neuroscience, & Emergency Medicine, University of Florida; [4]Departments of Neurology and Physiology/Pharmacology, SUNY-Downstate Medical Center; [5]Department of Neurosurgery, Baylor College of Medicine

Introduction: Neurofilament-light chain (NF-L) and phosphorylated neurofilament-heavy chain (pNF-H) have been reported as potential diagnostic and prognostic biomarkers in TBI. However, these proteins' longitudinal profiles and interrelationships in the acute and chronic time periods post-TBI are unclear.

Hypothesis: We hypothesized CSF and serum levels of NF-L and pNF-H are elevated after TBI and correlated with one another, and we posited NF-L and pNF-H levels are associated with disability and global neurological outcome after TBI.

Methods: We analyzed blood and CSF samples from two clinical cohorts (PITT and BC) with moderate-to-severe TBI. We obtained serum (n=233) and CSF (n=93) for day (D)0-6, and serum every two weeks for months 1-6 (PITT cohort). Disability Rating Scale (DRS) and Glasgow Outcome Scale-Extended (GOSE) were assessed at 6- and 12-months. We also included individuals from a clinical trial of erythropoietin post-TBI (BC cohort); we collected serum (n=99) and CSF (n=54) daily for 10D, and assessed 6-month DRS and GOSE.

Results: Serum NF-L and pNF-H gradually rise during the first week and peak 3-4 weeks post-injury. In the PITT cohort, mean NF-L and pNF-H were correlated within CSF ($r=0.44$; $p<0.0001$), D0-6 serum ($r=0.44$; $p<0.0001$), and month 1-6 serum ($r=0.38$; $p<0.01$). NF-L CSF, day 0-6 serum, and month 1-6 serum concentrations were higher among individuals with unfavorable GOSE and correlated with worse DRS ($p<0.05$, all comparisons). Higher pNF-H serum concentrations (D0-6/month 1-6), but not CSF pNF-H, were associated with unfavorable GOSE and worse DRS ($p<0.05$). In the BC cohort, higher D0-10 serum NF-L was associated with unfavorable GOSE ($p<0.01$) and worse DRS ($p<0.001$), but CSF NF-L and serum/CSF pNF-H were not correlated with outcome.

Conclusions: Neurofilament proteins peak 3-4 weeks post-TBI, and NF-L and pNF-H correlate within compartments. Serum NF-L is robustly associated with GOSE and DRS 6-12 months post-TBI.

Significance: These results provide basis for using neurofilament levels to monitor TBI recovery. Further study on clinical utility as prognosis and treatment-response indicators is needed.

Research/Grant Support: DoD W81XWH19-2-0012, NIDILRR 90DP004, CDC R49CCR23155, DoD W81XWH-071-0701, NIH T32HL134615

Abstract 22

DECISION TOOL FOR IDENTIFYING OUT OF HOSPITAL CARDIAC ARREST PATIENTS AT HIGH RISK FOR BRAIN DEATH

Coppler PJ,[1] Callaway CW,[1] Elmer J[1,2,3]

[1]Department of Emergency Medicine, University of Pittsburgh School of Medicine
[2]Department of Critical Care Medicine, University of Pittsburgh School of Medicine
[3]Department of Neurology, University of Pittsburgh School of Medicine

Introduction: Patients with return of spontaneous circulation after out of hospital cardiac arrest (OHCA) are often comatose secondary to anoxic brain injury. Some patients sustain severe injury and progress to brain death despite aggressive treatment. No validated decision rules identify patients at high risk of brain death.

Hypothesis: We hypothesized that arrest characteristics, qualitative and quantitative assessments of cerebral edema on presenting brain computed tomography (CT) and initial electroencephalography (EEG) predict brain death.

Methods: We identified comatose OHCA patients from our prospective registry who presented between January 1, 2010 to July 2019. We abstracted age, sex, arrest rhythm, arrest etiology, CPR duration, epinephrine doses, number of shocks; presenting, Pittsburgh Cardiac Arrest Category, motor exam and pupillary light reflex; brain CT grey to white ratio, sulcal effacement, and effacement of the basal cisterns; initial EEG background and suppression ratio. We used multiple imputation with chained equations with 10 imputations. We randomly partitioned date into 80% training set and 20% test set. We used Fast and frugal tree analysis to predict brain death, an approach that creates parsimonious, interpretable decision rules. Separately, we used adjusted logistic regression to build a saturated model and compared performance. We selected optimal sensitivity and specificity using Yoden's Index.

Results: We included 1566 OHCA patients, of whom 146 were declared brain dead. Fast and frugal tree analysis identified 3 strong sequential predictors of progression to brain death; absence of sulci on initial brain CT, and in cases without sulcal effacement, EEG background suppression and gray to white differentiation <= 1.23 had a sensitivity of 86% and specificity of 81% for predicting brain death. Logistic regression with all available predictors had better performance (sensitivity 95%, specificity 83%) but was a much more complex model.

Conclusions: Initial loss of sulci on brain CT or absence of EEG background with GWR<1.23 accurately predicts progression to brain death.

Significance: Early brain CT and EEG may aid clinicians in guiding early expectations of clinical trajectory for family, identify patients at high risk for clinical instability due to brain death physiology and optimize opportunities for organ donation evaluation.

Research/Grant Support: Dr. Elmer's research time is supported by the NIH through grant 5K23NS097629

Abstract 23

NOVEL METHOD FOR THE ASSESSMENT OF CAPILLARY STALLING AND THE NO-REFLOW EFFECT FOLLOWING CARDIAC ARREST

Gunasekaran V,[1] Stezoski J,[2] Simon D,[2] Nelson B,[1] Rowley A,[1] Wang P,[3] Manole MD,[1,2] Vazquez AL[3]

[1]Department of Pediatrics, Department of Critical Care Medicine, [2]Safar center for Resuscitation Research, [3]Department of Radiology, University of Pittsburgh

Introduction: Cortical hypoperfusion occurs after cardiac arrest (CA) and is associated with cerebral hypoxia, impaired metabolism, and impaired neuronal function, indicating that it precipitates a secondary brain injury. Capillary stasis, previously described in post-mortem preparations as the "no-reflow phenomenon", is present in 25% of cortical capillaries imaged using *in vivo* multiphoton microscopy after CA. Capillary stasis is currently quantified from videos of several sets of capillaries at baseline and serially post-CA. This method is inefficient, subjective to sampled capillary segments, and may not detect intermittent capillary stasis.

Hypothesis/Objective: To develop a novel method to assess of capillary stasis after CA that allows objective evaluation of capillary stasis over a larger cortical area based on red blood cell (RBC) flux variance. This method will be compared with previous RBC capillary flow measurements for the assessment of capillary stasis.

Methods: Three-month-old mice (n=5) underwent anesthesia with isoflurane, tracheal intubation, mechanical ventilation, and arterial and venous catheterization. A 4-mm craniotomy was created over the motor cortex, and a cover glass was cemented onto the skull for visual access to the brain. Asphyxial CA was induced by the cessation of mechanical ventilation for 5 minutes. Mice were resuscitated with chest compressions and epinephrine. The primary motor cortex was imaged using *in vivo* multiphoton microscopy at baseline and serially at 10-, 30-, and 60-min post-CA. Z-stacks were acquired in 3 μm steps in a 400x400x600μm field-of-view. Capillary stasis was assessed using two complementary techniques: RBC flow in nine capillaries/mouse, and RBC flux variance over the entire field. To quantify RBC flow, 30 sec time series were recorded at video rate in the same network of capillaries at baseline and post-CA, and RBC velocity was categorized as normal, sluggish flow, or stasis. Capillary RBC flux variance was acquired at 3 Hz for 2 min per location every 50 μm within the imaging region, and the variation in the signal produced by RBC flow in the capillaries was quantified as the coefficient of variation (RBC Flux Variance Index or RVI) and the RBC Concentration Index (RCI).

Results: All mice were resuscitated and survived to 60 min post-CA. Capillary stalling and stasis were observed post-CA in all imaged mice. We quantified the RBC Flux Variance Index (coefficient of variance) to assess signal fluctuations in capillary flow. The intensity of the capillary signal fluctuates as RBCs pass through them. We observed that the capillary flow is reduced post-CA due to intermittent stalling or arrested RBC flow in many capillaries. We noted the dynamic, intermittent nature of capillary flow post-CA. Hence, we represented normal capillary perfusion by orange or red color, and low, intermittent, or no perfusion by yellow, green, or blue color, respectively, and generated color flow maps for each mouse at each time point. We are currently quantifying the data and comparing the RBC flux with RBC flow.

Conclusion/Significance: In conclusion, RBC flux variance is a feasible, efficient, and objective method to evaluate capillary stasis.

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Abstract 24

ENHANCED ACCESS SERVICES ARE ASSOCIATED WITH DECREASED LOW-ACUITY PEDIATRIC EMERGENCY DEPARTMENT VISITS

Hincapie M,[1] Srinivasan S,[1] Alston K,[2] Butler G,[3] Ray K[4]

[1]Division of Pediatric Emergency Medicine, Children's Hospital of Pittsburgh
[2]University of Pittsburgh
[3]Division of Health Informatics, Children's Hospital of Pittsburgh
[4]Division of Pediatrics, Children's Hospital of Pittsburgh

Introduction: Despite programs to deter low-acuity emergency department (ED) visits, data indicate changes in access, cost, care expectations, and child health have led to decreased primary care visits and increased pediatric ED (PED) visits nationwide over the last 15 years. There is insufficient evidence on the role of enhanced access services (additional outpatient opportunities to receive care from primary care) to decrease low-acuity ED utilization.

Hypothesis: Patients from primary care offices with Enhanced Access Services have a decreased rate of Emergency Department utilization than primary care offices without Enhanced Access Services.

Methods: Using PED electronic health record data from a tertiary children's hospital, we identified low-acuity ED visits by children ≤18 years old between January 1, 2018-December 31, 2019 and assigned each visit to the child's primary care practice. We obtained active patient panel size from individual practices to calculate low-acuity ED visits rates per 100 active patients. Focusing on practices in the surrounding county, we stratified practices into tertiles of low-acuity ED visit rates (high, intermediate, and low). By practice tertile, we compared practice level patient demographics by rank-sum tests and enhanced access services by chi-square tests.

Results: Total PED encounters of 40,472 (by 25,354 unique patients) were attributable to 27 primary care practices (Fig. 1). Practice-level low-acuity ED visit rates ranged from 2 to 79 per 100 patients. Across tertiles, the median percent of low-acuity ED visits occurring during office hours (as opposed to outside of office hours) was highest in the high tertile practices (43.5%) compared to intermediate (41.9%) and low tertile practices (36.8%). Practice-level patient demographics (child age, race, gender) were similar (Table 1). Practices varied in percent of patients insured by Medicaid (median 52% of patients at high tertile practices vs 30% at low tertile practices, p=0.10). Practices in the highest tertile of ED utilization were less likely to have 4 or more evenings of weekday extended hours (11% vs. 55%, p=0.01) or any weekend hours (33% vs. 89%, p=0.03) (Table 2). Across all tertiles, similar proportion of practices reported same-day walk-in hours (89%, p=0.62).

Conclusions: Variation exists in enhanced access services throughout a county-wide sample of pediatric primary care practices. Practices with lower low-acuity PED utilization rates were more likely to offer four or more evenings of extended weekday hours and any weekend hours.

Significance: Enhanced access services is perceived to be beneficial to optimize outpatient care for low acuity visits, however, little is documented on this to date. By understanding rates of ED utilization by practice, this may inform and design implementation projects to address factors and barriers for local practices and their patients. It will also allow for opportunities to incorporate geographical information systems for further analysis on the census tract level.

Abstract 25

RESUSCITATION WITH EPINEPHRINE WORSENS CORTICAL MICROCIRCULATORY BLOOD FLOW AFTER EXPERIMENTAL PEDIATRIC CARDIAC ARREST

Oghifobibi OA,[1,6] Toader AE,[6] Alindogan NG,[6] Rowley A,[1,6] Nicholas MA,[1,6] Nelson BP,[1,6] Kline AE,[5,6] Nouraie SM,[2] Bondi CO,[5,6] Iordanova B,[3] Bayır H,[2,6] Clark RSB,[2,6] Loughran PA,[4,6] Watkins SC,[4,6] Kochanek PM,[4,6] Vazquez AL,[3] Manole MD[1,6]

[1]Department of Pediatrics, [2]Department of Critical Care Medicine, [3]Department of Radiology, [4]Department of Biology, [5]Department of Physical Medicine and Rehabilitation, [6]Safar Center for Resuscitation Research, University of Pittsburgh School of Medicine

Introduction: Epinephrine is the central therapy for the management of pediatric cardiac arrest (CA). Recent clinical data suggest that although epinephrine increases the return of spontaneous circulation (ROSC) and 30-day survival, it has no effect on survival to discharge with good neurological outcome. Moreover, several experimental studies suggest that epinephrine worsens cerebral ischemia, presumably secondary to reduction in microvascular flow. Here we characterize the effect of epinephrine on cortical microcirculation after pediatric asphyxial CA.

Methods: Postnatal day 16-18 rats (n=64) were used in four separate experiments to assess the effect of epinephrine vs. placebo (normal saline) administered at resuscitation on cortical perfusion as assessed by *in vivo* multiphoton microscopy and laser speckle flowmetry, cortical and thalamic brain tissue oxygenation (PbO_2), behavioral outcomes, and neuropathology. Rats received tracheal intubation, mechanical ventilation, and were randomized to receive epinephrine or placebo at resuscitation from a 9.5-min asphyxial CA.

Results: ROSC was achieved in all rats. The duration of CPR required to achieve ROSC was shorter after epinephrine vs. placebo. Epinephrine-treated rats had constriction of penetrating arterioles, increase in capillary stalling (no-reflow), and increase in capillary transit time of plasma through the cortex at 30-60 min post-ROSC vs. placebo. Placebo-treated rats had increased capillary diameters during the first 30-60 min post-ROSC. Both groups had similar decreases in overall cortical perfusion when measured using laser speckle flowmetry and similar cortical hypoxia from 15-60 min post-ROSC. Lastly, motor performance and spatial memory acquisition were similar between groups, but epinephrine-treated rats performed worse in the reference memory task vs. placebo. Hippocampal neuron counts did not differ between groups.

Conclusion/Significance: Treatment with epinephrine at resuscitation produces microvascular alterations during the first hour post-resuscitation, characterized by vasoconstriction, capillary stasis, prolonged cortical transit time, and absence of compensatory cortical vasodilation, which are associated with worse neurological outcome. Surprisingly, macrovascular perfusion and PbO_2 did not capture the microvascular effects of epinephrine. These results provide a platform for the development of strategies to mitigate the unwanted microvascular effects of epinephrine.

Research/Grant Support: HD075760, NS107785, NS121501, Children's Hospital of Pittsburgh Research Advisory Committee Award (Dr. Manole), NS117000 (Drs. Bayır, Clark), NS094404 (Dr. Vazquez), Children's Neuroscience Institute Award (Dr. Manole, Vazquez), 1S10OD025041-01 (Drs. St Croix, Watkins), Laerdal Foundation for Acute Medicine and The University of Pittsburgh's Physician-Scientist Institutional Award from the Burroughs Wellcome (Dr. Oghifobibi).

Abstract 26

PILOT VALIDATION OF AIRWAY HEMORRHAGE SIMULATION SCENARIOS

Schloss D,[1] Ashjaei A,[2] El-Khouri N,[3] Elias ME,[5] Lara-Gutierrez J,[4] Hardrick B,[5] Estock J,[5] Eibling D,[5] Duran T,[6] Alfaras-Melainis K,[6] Emlet L[5,6]

[1]Emergency Medicine Residency University of Pittsburgh, [2]VA Interprofessional Simulation Fellowship, PGY4, PGY2, [3]Emergency Medicine Residency University of Oklahoma Tulsa, PGY1, [4]General Surgery Residency UPMC Horizon, PGY2, [5]VA Pittsburgh Healthcare System [6]Department of Critical Care Medicine

Introduction: Airway hemorrhage is a challenging clinical situation faced by rapid response teams and emergency physicians, with an incidence of difficult airway intubation of 9-12% and complications that range from 4-28%. Simulation offers a teaching modality to facilitate education for high-risk, low frequency clinical situations.

Hypothesis: Creation of a simulator with airway hemorrhage capabilities in high fidelity airway scenarios (expanding post-surgical neck hematoma, oropPharyngeal hemorrhage, posterior nasopharyngeal epistaxis) for interprofessional management with deliberate practice would lead to ability to discriminate between performance after debriefing and formative feedback.

Methods: We recruited trainees in Emergency Medicine and Critical Care Medicine. We had 2 confederates (ME, DS, or AA) serving as RT and RN during all scenarios, which ran 5 minutes. Each subject underwent 3 versions of a simulation scenario within in one of our 3 types of airway hemorrhage cases (either hematoma, oropharyngeal hemorrhage or posterior nasopharyngeal epistaxis) in 1 hour, with no debriefing after scenario 1 (baseline), formative debriefing after scenario 2 (learning), and summative debriefing after scenario 3 (assessment). Post-simulation feedback was obtained for confidence, key learning point, and feedback for our scenario fidelity. Two anesthesiology-critical care (TD, SA) expert raters rated scenario 1 and 3 to look for performance difference in global rating (pass/ low pass/ fail) and items derived from previously validated NOTSS/ ANTS rating scales of non-technical skills. Interrater reliability, percent agreement, and intraclass coefficient were calculated for each type of scenario and overall between scenario 1 (pre) and scenario 3 (post).

Results: A total of 11 trainees participated, with high ratings (5-point Likert) of overall clarity (4.9), realism (4.7), and usefulness (4.9). Interrater reliability (IRR) of entire rating scale by expert raters varied per scenario, with nasopharyngeal at 0.78, oropharyngeal at 0.78, and neck hematoma at 0.65. Majority of trainees were Pass or Low Pass for all scenarios, with only 4 instances of a global rating of Fail (out of 36 total assessments).

Conclusions: We piloted 3 airway hemorrhage simulation scenarios to determine the ability of the scenarios to discriminate between performance before and after formative debriefing feedback. We found for even highly complicated advanced airway simulation the benefit of deliberate practice and reflection on key cognitive, skills, and team performance related to airway hemorrhage.

Significance: This pilot study validates these airway hemorrhage simulation scenarios as a modality for improving resident and fellow skills for complicated airway hemorrhage management through deliberate practice and reflection.

Research Support: 2019 Medical Education and Patient Safety Grant, Veteran's Research Foundation of Pittsburgh

Abstract 27

IMPROVED PUBLICATION RATE BY FELLOWS AFTER IMPLEMENTATION OF A COMPREHENSIVE RESEARCH CURRICULUM FOR PEDIATRIC EMERGENCY MEDICINE

Schmucker K,[1] Zuckerbraun N,[1] Vitale M,[1] Hickey R,[1] Callaway C,[2] Pitetti R,[1] Saladino R,[1] Manole M[1]

[1]UPMC Children's Hospital of Pittsburgh, Department of Pediatrics, Division of Pediatric Emergency Medicine
[2]UPMC Department of Emergency Medicine

Introduction: Pediatric subspecialty fellows are required to complete a scholarly product during training, but many never publish this work. Barriers to publishing are largely unknown but may be related to a lack of formalized research education and scholarly oversite.

Hypothesis: Implementation of an oversight program and a more comprehensive research curriculum increases the research expertise and productivity of pediatric emergency medicine fellows as measured by publication of scholarly work within three years of graduation.

Methods: This study was conducted at a tertiary children's hospital affiliated with an academic university, enrolling 3 fellows each year in its pediatric emergency medicine program. A scholarly oversight committee (SOC) was instituted at our program in 2007 to oversee the scholarly activities of the fellows. In 2011, we implemented a more comprehensive research curriculum to equip fellows with the tools for conducting and publishing research. To assess research productivity, we compared publication rate of our fellows before and after implementation of the curriculum. Graduated fellows also completed a survey scoring the value of their experiences completing their scholarly work. Results were scored on a 5-point Likert scale and compared using descriptive statistics.

Results: During the study period, 38 trainees completed the fellowship program. Publication rate increased from 29.7% (SD 14%) prior to implementation of the SOC and research curriculum to 91.5% (SD 17%) after implementation ($p < 0.01$, Mann Whitney U test). Graduated fellows expressed confidence in independently completing all surveyed research tasks. After implementation, there was a significant increase in how fellows scored the value of mentorship received mean score (4.3 vs 5, $p = 0.41$).

Conclusion: Implementation of a comprehensive research curriculum and oversight program significantly increased the rate of publication of scholarly work by fellows in a pediatric emergency medicine training program. Fellows reported confidence in their research abilities and improvements in quality of mentorship.

Significance: The structure and elements of the SOC and research curriculum may be replicated for fellows in other subspecialty programs.

Abstract 28

DEVELOPMENT OF NOVEL 20 HETE FORMATION INHIBITORS FOR NEUROTHERAPEUTICS

Seppi SK,[4] Tang C,[3] Kochanek PM,[2,4] Rowley A,[2,4] Nelson BP, Pitetti B,[4] Mathur A,[4] McDermott L,[3] Poloyac SM,[3,4] Manole MD[1,4]

[1]Department of Pediatrics, [2]Department of Critical Medicine, [3]School of Pharmacy, [4]Safar Center for Resuscitation Research, University of Pittsburgh

Introduction: 20-hydroxyeicosatetraenoic acid (20-HETE) is a vasoconstrictive metabolite of arachidonic acid produced by cytochrome P450 (CYP) 4A11 and 4F2 metabolism. We showed that 20-HETE levels increase in the brain following experimental pediatric cardiac arrest (CA), and that administration of a pre-clinical inhibitor of 20-HETE formation, HET0016, decreases 20-HETE levels, improves cerebral blood flow (CBF), and offers neuroprotection. Despite the robust neuroprotective effects of 20-HETE inhibition demonstrated by HET0016, there are no current inhibitors of CYP4-mediated 20-HETE formation available that are suitable for use in a clinical setting, as HET0016 has pharmacokinetics that are not suitable for clinical translation.

Hypothesis/Objective: To develop novel 20-HETE formation inhibitors suitable for human administration with good potency and favorable physicochemical properties: metabolic stability, selectivity, solubility, CYP inhibition, and blood-brain barrier (BBB) permeability.

Methods: Synthesis of 20-HETE inhibitors was performed by our medicinal chemists. To test the inhibitory efficacy of our battery of compounds we used microsomal incubates of human liver microsomes. The CYP450 metabolites were quantified using UPLC-MS/MS analysis. The levels of the preclinical candidate compound in brain and plasma and concentration of 20-HETE were then quantified in brain tissue samples and plasma samples using solid phase extraction and UPLC-MS/MS analysis in a triple quadrupole mass spectrometer.

Results: A battery of 143 novel compounds that inhibit 20-HETE formation were synthetized. After iterations of screening and in vitro evaluation of the 143 novel compounds, compound 107 was identified as a preclinical candidate that had strong potency and advantages of highly metabolically stable, wide selectivity window, and good brain penetration in vitro. Intravenous administration of 107 to pediatric rats showed that it penetrates BBB and reduces brain 20-HETE levels. Compound 107 penetrated the blood-brain barrier and exhibited a quick onset of brain 20-HETE inhibition in pediatric rats. Compound 107 exhibited a biphasic plasma concentration-time V profile after IV administration. It has a low clearance, an intermediate volume of distribution, and a relatively short half-life. We observed a biphasic decline of plasma and brain concentrations after 107 intravenous administration.

Conclusions: We identified a novel compound that inhibits 20-HETE formation and has suitable pharmacokinetics for clinical translation and will be advanced to in vivo efficacy assessment.

Significance: In future experiments will be to evaluate the pharmacodynamic efficacy of the best preclinical lead (107) vs. vehicle control administration in male and female CA rats under normothermic (37°C) or hypothermic (33°C) conditions. We will assess CBF, neuronal degeneration, and neurological outcomes as indices of efficacy.

Research/Grant Support: R33NS107785 (MDM), R01HD075760 (MDM), R21NS12150, Children's Neuroscience Institute (MDM, ALV).

BREAKOUT ROOM 5

Department of Neurological Surgery

Moderators	**Corina Bondi, PhD**
	Anthony Kline, PhD

Abstract #	Presenter
29	Katherine Fronczak
30	Lauren McFarlane
31	Hannah Radabaugh, PhD
32	Sarah E. Svirsky, BA
33	Hyunho Yoon

Abstract 29

REDUCED HIPPOCAMPAL ABUNDANCE OF SYNAPTIC VESICLE GLYCOPROTEIN 2 ISOFORMS FOLLOWING EXPERIMENTAL TRAUMATIC BRAIN INJURY

Fronczak K, Li Y, Parry M, Holetx E, Henchir J, Dixon CE, Carlson SW

Department of Neurosurgery, University of Pittsburgh School of Medicine

Introduction: Traumatic Brain injury (TBI) is a leading public health concern in the United States today, having been linked to long-term cognitive impairment, emotional disturbances, and increased risk for neurodegenerative diseases. Altered neurotransmission has been identified as a key pathological response contributing to impaired cognitive processing following brain trauma. Synaptic Vesicle glycoprotein 2 (SV2) has been recognized as critical for regulating neurotransmission by coupling Ca2+ signaling and maintenance of the readily releasable pool of vesicles in the pre-synaptic neuron, making it a promising target for an investigation of the effect of brain injury on neurotransmission. The goal of this study was to assess changes in the cortical and hippocampal abundance and localization of the two most well studied isoforms of SV2, SV2A and SV2B, following TBI in the rat brain.

Hypothesis: We hypothesized that TBI will alter the abundance of cortical and hippocampal SV2 isoforms.

Methods: To test this hypothesis, male rats ages 8-10 weeks were subjected to a severe controlled cortical impact (CCI) injury and sacrificed at 1, 3, 7, or 14 days post-injury. Immunoblotting and immunohistochemistry were completed to evaluate protein abundance and localization after 2.8mm CCI.

Results: SV2A and SV2B showed significant reductions in the cortex at several time points and in the hippocampus at all time points assessed following injury. Qualitative assessment of immunohistochemical corroborated reduced expression of isoforms shown by immunoblotting results.

Conclusions: These findings support the hypothesis that TBI results in altered abundance of SV2 isoforms.

Significance: These findings provide novel evidence for reduced cortical and hippocampal SV2 abundance in the days following injury and new insight into potential contributors to impaired synaptic communication and associated neurobehavioral dysfunction following TBI.

Research/Grant Support: NIH R21NS111099 (SWC), Chuck Noll Foundation (SWC) and The Pittsburgh Foundation (SWC)

Abstract 30

ASSESSMENT OF PROTEINS INVOLVED IN GLUTAMATE UPTAKE AND RELEASE IN A PEDIATRIC MODEL OF ASPHYXIAL CARDIAC ARREST

McFarlane LJ,[1] Nelson BP,[2] Rowley AP,[2] Seppi SK,[2] Alindogen NG,[2] Povysheva N,[3] Manole MD,[2] Carlson SW[1]

[1]Department of Neurological Surgery, [2]Department of Emergency Medicine, [3]Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA

Introduction: Cardiac arrest results in impaired neuronal function; however, the underlying mechanisms contributing to synaptic dysfunction are poorly understood. In the synapse, excitatory transmission is facilitated by the release of glutamate from docking presynaptic vesicles via the action of SNARE proteins. The excitatory amino acid transporters (EAATs) play a central role in tightly regulating and clearing glutamate from the synaptic cleft to prevent excitotoxicity and maintain neuronal communication. Previous work implicates that glutamate signaling is disrupted acutely after cardiac arrest; however, the mechanisms underlying altered excitatory neurotransmitter release have not yet been evaluated post-CA.

Hypothesis: We hypothesize that the disruption of intrasynaptic vesicular biology, and proteins involved in glutamate release and uptake, contribute to impaired neurobehavioral function following pediatric cardiac arrest.

Methods: To test this hypothesis, postnatal day 17 rats were subjected to 9.5-minute asphyxial cardiac arrest (n=9) or sham control surgery (n=6) and sacrificed at 7 days postinjury. Rapidly dissected hippocampi regions were processed for synaptosomal lysates. Hippocampal abundance of SNARE proteins: SNAP 25, SNAP 23, VAMP 2, synaptic vesicle proteins: synaptophysin, VGLUT1 and the glutamate transporter EAAT2 were assessed by immunoblot. Using immunohistochemistry, we evaluated the immunoreactivity of VGLUT1 and EAAT2. To complement our assessment of synaptic changes and to understand the neuropathology in this model we completed fluorojade staining and neurobehavioral analysis of motor performance.

Results: Immunoblotting revealed reduced hippocampal VAMP2 abundance in the cardiac arrest group compared to sham, but it did not reach significance ($p=0.078$). Assessment of all other proteins yielded no significant differences. Immunohistochemical staining and quantitative intensity measurements revealed no significant change in VGLUT1 or EAAT2 immunoreactivity in all hippocampal and cortical subregions.

Conclusions: Our results indicate that there is no overt change in the expression of the SNARE proteins and glutamate transporters of interest at the 7-day post-injury time point. VAMP2 exhibited a modest trend towards reduced abundance, suggesting presynaptic changes in this protein may contribute to altered presynaptic properties that can impair neurotransmitter release.

Significance: This study provides the first assessment of presynaptic proteins important for intrasynaptic vesicular properties and glutamate neurotransmission after pediatric CA. This improved understanding may aid in the identification of novel therapeutic targets that promote restoration of synaptic and cognitive function following pediatric cardiac arrest.

Support: NIH R33NS107785, R21NS121501 and Children's Neuroscience Institute (MDM). Children's Hospital of Pittsburgh Foundation and The Pittsburgh Foundation (SWC).

Abstract 31

MULTIVARIATE RECOVERY AFTER BRAIN INJURY DIFFERS BETWEEN DRUG THERAPIES AND MODEL USED: OPERATION BRAIN TRAUMA THERAPY

Radabaugh H,[1] Bonnell J,[1] Schwartz O,[1] Sarkar D,[1] Dixon CE,[2] Kochanek PM,[2] Dietrich WD,[1] Bramlett HM[1]

[1]University of Miami Miller School of Medicine, Miami FL
[2]Safar Center for Resuscitation Research, Pittsburgh, PA

Introduction: The impairments following traumatic brain injury (TBI) can be debilitating yet researchers have struggled to identify effective therapies. This is likely due, in part, to injury heterogeneity observed in the TBI population. It may be the case that univariate statistical analyses have missed informative patterns given that previous work from our group discovered that unsupervised machine learning (ML) algorithms can identify treatment effects overlooked by the original analyses (e.g. ANOVA). Furthermore, we found that supervised ML classifiers can distinguish which pharmacotherapy an animal received after fluid-percussion injury (FPI) following training on a preprocessed version of the Operation Brain Trauma Therapy (OBTT) dataset which contained metrics of recovery (i.e. physiology, motor, biomarkers, and cognition). Specifically, in all but one pairwise combination of minocycline (MIN), levetiracetam (LEV), erythropoietin (EPO), nicotinamide (NIC), or amantadine (AMT), the baseline was outperformed; the exception being NIC vs AMT.

Hypothesis: In the current study, we hypothesized that adapting the previously developed ML workflow to analyze an analogous dataset, the controlled cortical impact (CCI) portion of the OBTT study, would uncover that injury type dictates treatment effect.

Methods: Following the training and testing of 315 classifiers, this hypothesis was supported.

Results: The classifiers struggled to distinguish between treatment (50% prediction accuracy) in binary combinations of EPO, MIN, NIC, and AMT. LEV was the only treatment distinguishable from all other therapies (93-100%).

Conclusions: These results confirm that pharmacotherapies lead to unique recovery profiles following TBI and that these patterns are dependent upon injury model (i.e. FPI vs CCI).

Significance: Our data can serve as an informative component for designing translational studies with a higher potential for success (e.g., empirically determined patient grouping) and are a critical step towards identifying optimal treatments for specific subgroups of TBI patients.

Support: University of Miami U-LINK, DAMD W81HWH-14-2-0118 and W81XWH-10-1-0623

Abstract 32

RETINOIC ACID PRELIMINARY DOSE RESPONSE STUDY TO EXAMINE HIPPOCAMPAL SYNAPTIC PROTEIN EXPRESSION AND COGNITIVE FUNCTION AFTER TBI

Svirsky SE,[1,2] Henchir J,[2] Li Y,[2] Carlson SW,[2] Dixon CE[2,3]

[1]Center for Neuroscience, University of Pittsburgh, Pittsburgh, PA, [2]Department of Neurological Surgery, University of Pittsburgh Medical Center, Pittsburgh, PA, [3]VA Pittsburgh Healthcare System, Pittsburgh, PA

Introduction: Traumatic brain injury (TBI) is known to impair synaptic function, and subsequently contribute to observed cognitive deficits. Retinoic acid (RA), a metabolite of Vitamin A, has been identified as a potential pharmacotherapeutic for experimental ischemic injury and other neurological disorders, partially due to increased expression of proteins involved in synaptic signaling and plasticity. This study aims to understand the effect of various doses of RA on improving hippocampal synaptic protein expression and learning and memory behaviors after TBI.

Hypothesis: We hypothesize that RA will mitigate TBI-induced cognitive deficits and restore associated loss in synaptic protein expression, in a dose-dependent manner.

Methods: Under isoflurane anesthesia, adult male Sprague Dawley rats (275-300g, 9-10 animals per group) were subjected to either controlled cortical impact (CCI, 2.5mm deformation, 4m/s) or control surgery. Animals received daily intraperitoneal injection of 0.5, 1, 5, or 10 mg/kg body weight of RA or DMSO vehicle for 2 weeks. Animals underwent Morris Water Maze (MWM) testing 9-14 days after injury to evaluate spatial learning and memory. Expression of neurogranin (Ng), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), post-synaptic density protein 95 (PSD-95) and synaptophysin were evaluated in hippocampal whole cell and synaptosomal lysates by western blot at 2-weeks post-injury and normalized to β-actin.

Results: A two-way repeated measures ANOVA showed there was an overall group effect in MWM performance ($p=0.002$). Post-hoc analysis revealed a significant injury effect between Sham and CCI vehicle groups ($p=0.008$). No significant difference between Sham-vehicle and CCI- 0.5, 1 and 5mg groups was observed, suggesting a moderately positive effect of RA. A one-way ANOVA of synaptosomal Ng and CaMKII protein expression showed an overall group effect ($p=0.0057$, $p<0.0001$, respectively). Similarly, post-hoc analysis showed a significant injury effect between Sham and CCI vehicle groups ($p=0.009$, $p=0.0025$, respectively), but no significant difference between Sham-vehicle and CCI-1 and 5mg groups. Interestingly, the 10mg dose was comparable to the CCI-vehicle dose, demonstrating a potential deleterious effect. No other post-hoc comparisons were significant.

Conclusions: RA had a modestly positive effect on both behavior and hippocampal synaptic protein expression, with doses demonstrating similar effects across behavioral and biochemical outcomes. Further work is needed to investigate the mechanisms of RA signaling in TBI-induced cognitive dysfunction, particularly given the pleiotropic effects of RA on the CNS.

Significance: Understanding the benefit of RA on posttraumatic cognitive deficits in experimental TBI may lead to rapid translation for the evaluation of RA in patients with TBI. Furthermore, understanding the relationship between synaptic protein expression and behavior, may further elucidate mechanisms of TBI-induced impairments of synaptic function and plasticity.

Grant Support: Children's Hospital of Pittsburgh of the UPMC Health System (SES), NIH R01-NS106925, NIH R21-NS115440, and PA Department of Health grant 4100077083 (CED).

Abstract 33

EFFECTS OF TRAUMATIC BRAIN INJURY ON DENDRITIC ARBORIZATION IN HIPPOCAMPAL CA1 NEURONS

Yoon H, Henchir J, Svirsky S, Parry M, Carlson SW, Dixon CE

Department of Neurological Surgery, University of Pittsburgh; Safar Center for Resuscitation Research

Introduction: Impairment in the hippocampus, and thus memory function, is a notable sequela of traumatic brain injury (TBI). In previous studies, a decrease in the number of synapses within the cornu Ammonis 1 (CA1) of the hippocampus following TBI was found in rats. To further elucidate the cellular mechanisms that underlie the effects of TBI on hippocampal function, this study examined the changes to CA1 dendritic arborization in rats 4 weeks following controlled cortical impact (CCI).

Hypothesis: We hypothesized that there would be a decrease in the complexity of CA1 dendritic arborization at 4 weeks post-injury in rats that received CCI compared to rats who received sham control surgery.

Methods: Adult male Sprague-Dawley rats were randomly divided into CCI and Sham control groups, wherein the CCI group underwent an 8 mm craniectomy (centered at AP: +4.0 mm, L: +2.8 mm from lambda) to expose the dura for the CCI injury (2.6 mm depth at 4 m/s for 150 msec dwell time with a 6 mm impactor tip), and the Sham control group underwent all surgical procedures and received a craniectomy only. At 4 weeks post-injury rats were euthanized and the brains prepared for the Golgi staining process. Images of Golgi-stained CA1 neurons were reconstructed into 3-dimensional computer models using Neurolucida 360. Branch order was determined as follows: dendritic segments directly branching from the soma were labeled as "primary," segments branching from primary branches as "secondary," and so on. The Neurolucida 360 data output was analyzed using SPSS.

Results: An overall decrease in number of neurons in CA1 was observed in the CCI group compared to sham control. However, Sholl analysis of the surviving neurons in the CCI condition showed an increase in number of dendritic branching compared to the sham control condition ($p<0.05$). This difference was driven by an increase in higher-order branching ($p<0.001$) – i.e. tertiary branching and above – and not by lower order branches, i.e. primary ($p=0.786$) and secondary ($p=0.990$). Further breakdown analysis revealed this increased branching was seen in both apical ($p=0.027$) and basal ($p<0.0005$) dendrites. The effect of higher order branching was present in both apical ($p<0.0005$) and basal ($p<0.0005$) dendrites.

Conclusions: There was greater complexity overall in the dendritic arborization of CA1 neurons post-CCI as compared to neurons post-sham control. The effect was mainly driven by the change in higher order (≥tertiary) dendritic branching.

Significance: Contrary to our hypothesis, dendritic arborization increased in neurons subjected to CCI. One explanation could be that with a chronic time course, there is a process of plasticity in CA1 that involves increased branching in an attempt to restore the lost connections and compensate for the initial loss of CA1 neurons and synapses. Further study of dendritic spine morphology in these neurons may help elucidate the mechanism behind the increased branching.

Research/Grant Support: University of Pittsburgh School of Medicine Dean's Summer Research Project; The Walter L. Copeland Fund of The Pittsburgh Foundation, the Pennsylvania Department of Health, PA Consortium on TBI (PACT) grant 4100077083 and the Department of Neurological Surgery Neurotrauma Chair endowment.

BREAKOUT ROOM 6

Department of Physical Medicine & Rehabilitation

Basic Science

Moderators **Robert Clark, MD**

Yan Xu, PhD

Abstract #	**Presenter**
34	Iya Cooper
35	Eleni H. Moschonas, BS, BA
36	Tyler Shick, BS
37	Beate Wehrmeyer, BSc

Abstract 34

EVALUATING THE EFFICACY OF MUSIC TO PROMOTE NEUROBEHAVIORAL AND COGNITIVE RECOVERY AFTER BRAIN TRAUMA

Cooper I,[1,2] Vozzella V,[1,2] Moschonas E,[1-4] Cheng J,[1,2] Jarvis J,[1,2] Fink E,[2,5] Bondi CO,[1-4] Kline AE[1,2,4]

[1]Physical Medicine & Rehabilitation
[2]Safar Center for Resuscitation Research
[3]Neurobiology, [4]Center for Neuroscience, [5]Pediatric Critical Care Medicine
University of Pittsburgh, Pittsburgh, PA

Introduction: Traumatic brain injury (TBI) is a leading cause of death and disability for children and adults worldwide. In the USA there are approximately 2.8 million TBI-related emergency department visits each year. The majority of TBI survivors have long-lasting disturbances in motor, cognitive, and emotional health (e.g., anxiety) that negatively impact their long-term academic, occupational, and social functioning. Despite the individual, medical, and societal burden of TBI, interventions to remediate the TBI sequelae and promote recovery are lacking and/or have not successfully translated from the bench to the hospital, thus strongly supporting the need to test and implement novel, safe, effective, nonpharmacological strategies. Music holds untapped potential for improving cognition and neurobehavior after TBI as evidenced by clinical studies in adults with brain injury where music-based interventions were associated with improved physical, cognitive, and emotional functioning. Basic science data in non-TBI rats also show that music enhances cognition. The aim of this study was to increase our understanding of how music affects the brain when used as a therapy to confer cognitive and neurobehavioral recovery after TBI.

Hypothesis: Classical music provided to adult rats after TBI will ameliorate TBI-induced deficits in cognition and neurobehavior.

Methods: Adult male rats received a TBI of moderate severity, or sham injury, and 24 h later were randomized to classical or no music (i.e., ambient room noise), which consisted of exposure for 3 h/day from 7:00 pm to 10:00 pm (rat awake period) for 32 days (last day of behavior). Motor (beam), cognitive (spatial learning and executive function), anxiety-like behavior (open field and shock probe defensive burying), histology (lesion volume), and Iba1 were evaluated. The behavioral data were analyzed by two-way ANOVAs with repeated measures over testing days, followed by the Newman-Keuls post-hoc test, which corrects for multiple comparisons.

Results: Our preliminary data (5 per group) showed that classical music improved motor, cognitive, and anxiety-like behavior, reduced lesion volume, and increased Iba1+ staining vs. no-music.

Conclusions and Significance: These preliminary findings support the role of music as a beneficial therapy for TBI that can be implemented by the 8000 certified music therapists in the USA.

Research/Grant Support: Supported in part by NIH grants HD069620, NS099674, NS08496 (AEK), NS094950, NS099683, NS110609 (COB) and T32 NS007433-22 to Alan Sved (EHM)

Abstract 35

EFFECTS OF POSITIVE ALLOSTERIC MODULATION OF A7 NICOTINIC ACETYLCHOLINE RECEPTORS ON SUSTAINED ATTENTION AND CHOLINERGIC NEUROTRANSMISSION AFTER EXPERIMENTAL TRAUMATIC BRAIN INJURY

Moschonas EH,[1-3] Race N,[1,2] Rennerfeldt P,[1,2] Reddy R,[1,2] Sunleaf C,[1,2] Wehrmeyer B,[1,2] Ranellone T,[1,2] Patel A,[1,2] Benbourenane A,[1,2] Balaji S,[1,2] Magdelinic T,[1,2] Sha S,[1,2] Cheng JP, [1,2] Carlson SW,[1-2,4] Dixon CE,[1-6] Kline AE,[1-3,7-9] Bondi CO[1-4]

[1]Physical Medicine & Rehabilitation, [2]Safar Center for Resuscitation Research, [3]Center for Neuroscience, [4]Neurobiology, [5]Neurological Surgery, [6]Anesthesiology, [7]Center for the Neural Basis of Cognition, [8]Critical Care Medicine, [9]Psychology, University of Pittsburgh, Pittsburgh, PA, United States

Introduction: Traumatic brain injury (TBI) is a leading cause of cognitive disability worldwide. Impaired attention and memory are due, in part, to TBI-induced cholinergic dysregulation, which suggests that pharmacological strategies that amplify activation of acetylcholine (ACh) receptors may ameliorate behavioral deficits.

Hypothesis: NS-1738, a novel type-I positive allosteric modulator (PAM) at the α7 nicotinic ACh receptors (α7 nAChRs) will normalize cholinergic neurotransmission and restore sustained attention after TBI.

Methods: Prior to surgery, all rats were trained on the abbreviated 3-choice serial reaction time task (3-CSRT), which requires 80% accuracy using a 2-s cue presentation. Isoflurane-anesthetized adult male rats received either a controlled cortical impact (CCI) of moderate severity (2.8 mm cortical deformation at 4 m/s) or sham injury (i.e., no impact) and then were randomly assigned to NS-1738 (3 mg/kg) or vehicle (1.0 mL/kg). Treatments began 24 h after surgery and were given once daily for 7 days. Assessment of sustained attention, which consisted of percent accuracy, percent omissions (i.e., distractibility), and premature responses (i.e., impulsivity) was performed on days 14-24. On post-injury day 30, markers of cholinergic neurotransmission such as acetylcholinesterase (AChE), choline acetyltransferase (ChAT), and α7 nAChRs were examined in the medial prefrontal cortex (mPFC), a region previously implicated in mediating sustained attention via Western blot. The data were analyzed by two-way ANOVAs with repeated measures over testing day, followed by Newman-Keuls post hoc tests when appropriate.

Results: Deficits on sustained attention, demonstrated by decreased percent accuracy and increased percent omissions, in the 3-CSRT were observed after TBI relative to the pooled sham group. Subacute NS-1738 did not improve accuracy or omissions when compared to the vehicle-treated TBI group ($p>0.05$). The lack of differences may have resulted from a drug wash-out period. Noteworthy, sham rats displayed increased impulse control in premature responding relative to both TBI groups (vehicle and NS-1738), which suggests that TBI hinders progressive impulse control and may have major clinical implications. Preliminary Western-blot analysis reveals a general injury effect toward the reduction of cholinergic modulation after TBI.

Conclusions: The data suggest that subacute augmentation of cholinergic modulation via NS-1738 after TBI in adult male rats was not effective in restoring higher-order attention long-term, which does not support the hypothesis. Ongoing studies in our laboratory are evaluating the possibility that a chronic dosing paradigm may improve cognitive function after experimental TBI.

Significance: To date, there are no FDA approved pharmacotherapies for the amelioration of TBI-induced cognitive deficits. Hence, examining the efficacy of NS-1738 after experimental TBI is imperative to improve translatability of pharmacological interventions.

Research/Grant Support: NIH NS094950, NS099683, NS110609 (COB), the UMPC Rehabilitation Institute pilot grant (COB), and NIH T32 NS007433-22 (EHM)

Abstract 36

INTERLEUKIN 7 REGULATES ADAPTIVE IMMUNITY AND PROMOTES NEURORECOVERY AFTER MODERATE TO SEVERE TRAUMATIC BRAIN INJURY

Shick TJ,[1,2] Vaughan LE,[1] Gober I,[1,2] Russell AL,[1,2] Vagni V,[2,3] Kochanek PM,[2,3] Wagner AK[1,2,4]

[1]Department of Physical Medicine and Rehabilitation, University of Pittsburgh
[2]Safar Center for Resuscitation Research, University of Pittsburgh
[3]Department of Critical Care Medicine, University of Pittsburgh
[4]Center for Neuroscience, University of Pittsburgh

Introduction: TBI produces a robust pro-inflammatory response and cellular immunity derangements, which we hypothesize may be relevant to function and adaptive immunity long-term. Our previous findings suggest elevated IgM autoantibodies to the pituitary and/or hypothalamus may support neurorepair in a clinical TBI population.

Hypothesis: Since Interleukin 7 (IL-7) has a role in lymphoproliferative processes and antibody production, we hypothesize that recombinant humanized (rh)IL-7 may be neuro-reparative post-TBI.

Methods: Adult male C57BL/6 mice (n=70) underwent either Sham (n=19) or Controlled Cortical Impact (CCI; n=51) (2mm deformation, 6m/s). On experimental day (ED) 1, 7, and 13 post-surgery, subcutaneous injections of vehicle, low dose rhIL-7 (LD; 0.5μg), or high dose rhIL-7 (HD; 5μg) were given to Sham or CCI mice (n=17-19/group).

Results: Motor testing (wire grip) on ED1-5 showed that TBI-impaired motor strength was improved only with LD rhIL-7 treatment ($p<0.05$). In the elevated plus maze (ED10), LD and HD rhIL-7 treatment attenuated TBI-related anxiety as shown by increased number of open arm entries. In addition to improved Morris water maze (MWM) performance (ED14-18 acquisition latencies, thigmotaxis suppression, and D19 time in target zone for long-term memory probe trials) ($p<0.05$), rhIL-7 also improved D19 visible platform testing ($p<0.1$). Tissue and blood were collected (ED21), and flow cytometry forward scatter revealed a significant reduction in blood and spleen lymphocytes post-TBI that was partially (spleen; $p<0.1$) or significantly (blood; $p<0.05$) restored with HD rhIL-7 treatment. Serum adaptive (IL-2, IFNγ) and innate (MIP-1a/b, GM-CSF) markers were suppressed after CCI (Luminex) and partially recovered with HD rhIL-7 treatment. There were treatment specific correlations between innate and adaptive immune markers and D19 probe trial performance testing long-term memory.

Conclusions: Moderate to severe TBI causes lymphopenia and behavioral deficits, which can be significantly improved via intermittent treatment with rhIL-7**.** Overall, our data suggests that rhIL-7 may support post-CCI functional recovery.

Significance: Future work should focus on inflammatory mechanisms of repair underlying improved function with rhIL-7 treatment and will provide a biomarker-based mode to studying IL-7 treatment in a clinical population of TBI.

Research/Grant Support: UPP Foundation, UPMC Rehabilitation Institute, Centre for Neuro Skills (PI: Amy K. Wagner, MD).

Abstract 37

BEHAVIORAL DIFFERENCES IN ADOLESCENT RATS DURING INSTRUMENTAL LEARNING AND ATTENTIONAL SET-SHIFTING: A COMPARISON OF TWO MODELS OF PEDIATRIC TBI

Wehrmeyer B,[1,2] Moschonas EH,[1-3] Rennerfeldt P,[1,2] Reddy R,[1,2] Ranellone T,[1,2] Balaji S,[1,2] Ramanan H,[1,2] Cheng JP,[1,2] Kline AE,[1-3,5-7] Bondi CO[1-4]

[1]Physical Medicine & Rehabilitation, [2]Safar Center for Resuscitation Research, [3]Center for Neuroscience, [4]Neurobiology, [5]Center for the Neural Basis of Cognition, [6]Critical Care Medicine, [7]Psychology, University of Pittsburgh, Pittsburgh, PA, United States

Introduction: Traumatic brain injuries (TBIs) account for 500,000 emergency room admissions of children in the USA yearly. Survivors have a higher risk of repeated mild insults or concussions (rmTBIs), which can lead to delayed development as well as enhanced propensity for attentional and mood disorders. Preclinical models of attention after TBI have not been cross-referenced among different injury types, leaving the possibility that injury modality may differentially alter behavior.

Hypothesis: Adolescent rats will display impaired goal-directed behavior and executive dysfunction after pediatric brain trauma whether produced by repeated concussions or moderate focal injury.

Methods: To test the hypothesis, we compared behavioral assays (goal-directed behavior, motivation, and attention) in adolescent rats following rmTBIs [closed-head injury, daily on postnatal days (PND) 17-19, 1 mm depth at 4 m/s] versus a one-time controlled cortical impact (CCI) (focal injury, PND 17, 2.2 mm cortical depth at 4 m/s) as pediatrics. Motivation-based behavior was measured through an instrumental learning task (ILT) over 12 training days during adolescence and commencing two weeks post injury. Behavioral flexibility was tested by a digging-based attentional set-shifting test (AST) with increasingly difficult contingencies for a food reward. The data were analysed using repeated-measures ANOVAs, followed by the Newman-Keuls post hoc tests, which corrects for multiple comparisons.

Results: The ILT revealed no significant behavioral changes between CCI and rmTBI groups. However, adolescent rats in both TBI groups completed more total trials, made fewer task-irrelevant pokes, had shorter cue-to-poke and poke-to-reward retrieval latencies compared to sham rats (p's<0.05), which is contrary to our hypothesis that TBI rats would underperform. In AST, no differences were found between CCI and rmTBI rats, or between TBI groups and Sham rats.

Conclusions: ILT findings suggest divergent interpretations, such as enhanced motivation, yet reduced multi-tasking and exploratory behavior in adolescent rats after pediatric TBI. The absence of differences between CCI and rmTBI, or between TBI groups and Sham rats in AST is likely due a well-described cognitive rigidity and higher baseline exhibited by adolescents on this task.

Significance: Further research using clinically-relevant injury modalities to predict post-injury behavioral symptoms in survivors of childhood TBIs is warranted.

Research/grant support: NIH NS094950, NS099683, NS110609 (COB), Research Advisory Committee at Children's Hospital of UPMC (COB), and NIH T32 NS007433-22 to A. Sved (EHM)

BREAKOUT ROOM 7

Department of Physical Medicine & Rehabilitation

Clinical/Health Services

Moderators **Christopher Horvat, MD, MHA**

Ajay Wasan, MD, MSc

Abstract #	Presenter
38	Nabil Awan, MS
39	Claudia Bianchine and John Maczuzak
40	Jessica Jarvis, PhD
41	Marina Levochkina, BS
42	Luca Shanley

Abstract 38

PREDICTING POST-TRAUMATIC EPILEPSY AFTER MODERATE-TO-SEVERE TRAUMATIC BRAIN INJURY

Awan N,[1,2] Kristen B,[1,3] DiSanto D,[1] Kumar R,[4] Juengst S,[5] Harrison-Felix C,[6] Dams-O'Connor K,[4] Pugh M,[7,8] Zafonte R,[9] Walker W,[10] Szaflarski J,[11] Krafty R,[2,12] Wagner A[1,13-15]

[1]Physical Medicine & Rehabilitation, University of Pittsburgh, Pittsburgh, PA
[2]Biostatistics, University of Pittsburgh, Pittsburgh, PA
[3]School of Medicine, University of Pittsburgh, Pittsburgh, PA
[4]Rehabilitation & Human Performance, Icahn School of Medicine at Mount Sinai, New York, NY
[5]Physical Medicine and Rehabilitation and Applied Clinical Research, University of Texas Southwestern, Dallas TX
[6]Craig Hospital, Denver CO
[7]University of Utah Health Sciences Center, Salt Lake City UT
[8]Salt Lake City VA Health System, Salt Lake City UT
[9]Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA
[10]Physical Medicine & Rehabilitation, Virginia Commonwealth University
[11]Neurology, University of Alabama at Birmingham Epilepsy Center, Birmingham, AL
[12]Biostatistics and Bioinformatics, Emory University, Atlanta, GA
[13]Neuroscience, University of Pittsburgh, Pittsburgh, PA
[14]Center for Neuroscience at University of Pittsburgh, Pittsburgh, PA
[15]Clinical and Translational Science Institute, University of Pittsburgh, Pittsburgh PA

Introduction: Risk for developing post-traumatic seizure/epilepsy (PTS/PTE) after traumatic brain injury (TBI) is high, yet standard risk assessments for PTS/PTE are not readily available. We used the TBI Model Systems National Database (n=5,371) to develop a free app for PTS/PTE prediction to help clinicians with PTE prognostication, prevention, and management as well as inclusion in clinical treatment trials.

Hypothesis: We hypothesized that parsimonious prediction models could satisfactorily quantify individual seizure risk over the first two years after moderate-to-severe TBI (msTBI).

Methods: We utilized clinical, demographic, and imaging data as covariates and developed two cumulative 2-year PTS models using baseline factors (+/- acute hospital seizure status), and two year-2 PTS models evaluating new +/- recurrent seizures during year 2 using Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression.

Results: A maximum shrinkage within one standard deviation of the maximum area under the curve (AUC) produced parsimonious models with craniectomy, craniotomy, intracranial fragments, subdural hematoma, contusion, acute seizure, acute length of stay, pre-injury drug use, pre-injury psychiatric hospitalization, and year-1 seizure status (for year-2 PTS only) as the most important predictors across different models. The baseline model (with acute hospital seizure status incorporated) had an average sensitivity of 72.07%, specificity of 62.16%, and AUC of 73.02% across the 5-fold cross-validation (CV). The Year-2 Model evaluating risk for both new and recurrent year 2 seizures had an average sensitivity of 86.43%, specificity of 60.26%, and AUC of 85.04%.

Conclusions: The prognostic models can translate into useful clinical tools for PTS prediction.

Significance: Predictive factors were identified using information readily available during admission and acute care hospitalization, which have important implications for participant inclusion into RCT as well as PTE prevention and management. Individual risk can be modeled using the freely available online risk calculator found at https://wagnerlab.shinyapps.io/wagnerlab_posttbi_seizureprediction_app/

Research/Grant Support: DoD: W81XWH1810736 NIDILRR: 90DP0041 Wagner AK., PI

Abstract 39

NON-NEUROLOGICAL ORGAN DYSFUNCTION IMPACTING GLOBAL OUTCOMES IN MODERATE-TO-SEVERE TBI SURVIVORS

Bianchine C,[1*] Maczuzak J,[1*] Levochkina MS,[1,2] Trombley SP,[1] Vaughan LE,[1] Wagner AK[1,3,4]

[1]Department of Physical Medicine and Rehabilitation, University of Pittsburgh
[2]Department of Infectious Diseases & Microbiology, University of Pittsburgh
[3]Safar Center for Resuscitation Research, University of Pittsburgh
[4]Clinical and Translational Science Institute, University of Pittsburgh
[*]Denotes co-first authors

Introduction: One of the leading causes of mortality and disability in the United States is traumatic brain injury (TBI). Non-neurological Organ Dysfunction (NNOD) has been shown to lead to acute unfavorable outcomes in patients of TBI, yet chronic outcomes have seldom been investigated.

Hypothesis: We hypothesized that patients who develop NNOD during their initial hospitalization would have poorer outcomes at six-months post-TBI.

Methods: With patient interviews and the local trauma registries, we collected clinical, demographic, and injury severity variables on (n=349) moderate-to-severe TBI patients. Using electronic medical records out to three weeks post-injury, we collected and scored daily lab values based on five Sequential Organ Failure Assessment (SOFA) score non-neurological domains: respiratory, measured by PaO_2/FiO_2, renal, measured by creatinine, hepatic, measured by total bilirubin, coagulation, measured by platelets, and cardiovascular, measured by Mean Arterial Pressure and Inotrope administration. Outcomes were assessed at six-months post-injury using the Glasgow Outcome Scale (GOS) which was then further dichotomized into (1) favorable (GOS=3,4) and (2) unfavorable outcomes (GOS=3,4). Using peak SOFA score over the three weeks for each organ system domain, we assessed NNOD's relationship to six-month outcome using multivariate logistic regressions, adjusting for age, sex, Injury Severity Scale (ISS), and Computer Tomography brain lesion burden.

Results: We found that cardiovascular dysfunction (OR=1.51, p=0.0342), was significantly related to poor outcome while respiratory (OR=1.32, p=0.0617), renal (OR=1.49, p=0.0568), and hepatic dysfunction (OR=1.37, p=0.0895) were trending in the associations. Coagulation dysfunction, when adjusted for all covariates, had no association with poor outcome (p=0.234)

Conclusions: Our results demonstrate that the development of NNOD not only impacts acute outcomes, but also has implications into the chronic phase of recovery further highlighting the systemic manifestations of TBI.

Significance: This confirms our hypothesis that non-neurologic organ dysfunction leaves lasting impacts on patients suffering from TBIs highlighting the importance of preventative measures against organ dysfunction development.

Abstract 40

FEASIBILITY OF A MUSIC THERAPY INTERVENTION FOR MECHANICALLY VENTILATED CHILDREN IN THE PEDIATRIC INTENSIVE CARE UNIT

Jarvis J,[1] Robb S,[2] Houtrow A,[1] Treble-Barna A,[1] Rubin P,[3] Kochanek P,[3] Fink E[3]

[1]Department of Physical Medicine & Rehabilitation, University of Pittsburgh School of Medicine
[2]Department of Nursing, Indiana University School of Nursing
[3]Department of Critical Care Medicine, University of Pittsburgh School of Medicine

Introduction: Children requiring mechanical ventilation (MV) in the pediatric intensive care unit (PICU) are at increased risk of stress and pain. Standard of care to alleviate stress and pain in the PICU is a pharmacologic-focused approach, which is associated with increased risk of delirium and debilitation. Listening to recorded music during MV in adults decreases stress, pain, and medication requirements. However, data needed for a PICU music intervention are lacking. The objectives of this single-group trial were to (1) determine feasibility of providing live music by a music therapist during MV in the PICU and of completing proposed data collection, and (2) to obtain stakeholder feedback on intervention acceptability and optimizations prior to a scale-up trial.

Hypothesis: The music therapy intervention and trial design will be feasible and acceptable for families of critically ill children requiring MV.

Methods: This mixed-methods, single-group feasibility trial enrolled 20 families and their children aged 2 months – 17 years old who required invasive or noninvasive MV with anticipated PICU length of stay > 72 h. Following informed consent, children received a 20-minute music therapy session 3x/week until they either returned to baseline respiratory status or for 2 weeks, whichever came first. Music therapists provided live music (singing with guitar accompaniment) of child preferred songs, in a calming manner (60-80 beats per min; low, steady volume). Data collection included saliva- and physiologic-based biomarkers of child stress and pain, patient reported outcome (PRO) on caregiver anxiety pre/post music therapy interventions, nurse-reported delirium and pain scores, and PRO on child emotional health at PICU discharge. Semi-structured interviews were conducted with caregivers to ascertain their perception of intervention benefits, limitations, and optimizations. We assessed feasibility via recruitment rate, protocol adherence, and data collection completeness.

Results: We screened 1,000 children admitted into the PICU from June 2020-February 2021. Of 29 children that met inclusion criteria, 20 (69%) were enrolled. Median (IQR) PICU days to enrollment was 5.5 (3.3-7.0) days and children received a median (IQR) of 2.5 (2.0-4.0) live music therapy sessions. Saliva and physiologic-based biomarker data were 88% and 96% complete, respectively. PRO data completion ranged from 64-88%. Intervention protocol adherence was 100%. During qualitative interviews (n=15), caregivers frequently stated the music therapy was calming for the child and themselves and the duration (20 min) was adequate, but that the session frequency (3x/week) was inadequate. Some caregivers suggested providing families with recorded music playlists to supplement between music therapy sessions as needed.

Conclusions: Our preliminary findings suggest enrollment and adherence to a music therapy intervention was feasible and acceptable to families of children treated with MV in the PICU. Future trials should explore increasing dose via a combined live and recorded music approach.

Significance: Music therapy warrants further investigation as a potential nonpharmacologic approach for decreasing critically ill children's stress and pain.

Research / Grant Support: NIH T32 HD040686 (Jarvis), NIH K01 HD097030 (Treble-Barna), The Lloyd Reback Family Gift (Jarvis).

Abstract 41

TEMPORAL DYNAMICS OF NEUTROPHIL-TO-LYMPHOCYTE LEVELS AND INFECTIONS AFTER TRAUMATIC BRAIN INJURY

Levochkina M,[1,2] Vaughan L,[1] Awan N,[1] Fan E,[1] Wagner A[1,3,4]

[1]Department of Physical Medicine and Rehabilitation, University of Pittsburgh
[2]Department of Infectious Diseases & Microbiology, University of Pittsburgh
[3]Safar Center for Resuscitation Research, University of Pittsburgh
[4]Clinical and Translational Science Institute, University of Pittsburgh

Introduction: More recently, the prognostic value of Neutrophil-to-Lymphocyte Ratio (NLR) has been explored in the traumatic brain injury (TBI) literature however, to date, no studies have considered the implications infections have on NLR levels in the TBI population.

Hypothesis: We predicted that NLR captures a unique cellular immune profile that both influences and is influenced by infections acquired post-TBI.

Methods: We collected demographic, clinical, and outcome data on patients with moderate-to-severe TBI (n=196). Daily infection data, lowest absolute (ABS) lymphocyte levels, and highest ABS neutrophil levels were collected from electronic medical records throughout 21 days post-TBI, while demographic and injury severity variables were collected from patient interviews and the local trauma registry. Infection status was assessed using culture reports. We utilized group-based trajectory (TRAJ) analysis to represent the dynamics of NLR levels over time and to stratify individuals into low and high subgroups. We utilized change-point analysis of mean NLR levels to determine the optimal point of change to create two-time epochs of interest. Within those time epochs, a mixed-effects cox regression analysis to assess both NLR's impact on time-to-infection and, the reverse, infection's impact on. All analyses were adjusted for Glasgow Coma Scale (GCS), Injury Severity Score (ISS), and Computer Tomography (CT) Burden.

Results: Trajectory analysis found optimal two group models for neutrophils (*high* n=121, *low* n=75), lymphocytes (high n=121, low n=75), and NLR (*high* n=67, *low* n=129). The change-point algorithm found day 5 as the optimal point of change in mean NLR levels over time making our two epochs of study: (1) day 0-5 and (2) day 6-20. We found that, for day 0-5, high NLR TRAJ (p=0.0409) and low Lymphocyte TRAJ (p=0.0378) group-membership increased odds of acquiring an infection early in the time course while high Neutrophil TRAJ was not related to infection (p=0.3634). During the first-time epoch, infection status was loosely related to increasing NLR levels (p=0.0973) however, for day 6-20, infection status was highly significantly related to increased levels of NLR (p=<0.0001).

Conclusions: Using mixed-effects regression modeling techniques that adjust for time, allowed us to identify early in the time course, a state of lymphopenia post-TBI that contributes to increased infection rates and which reflects the initial high NLR levels. Later in the time course, however, primary infections and subsequent neutrophilia contributes to increased NLR levels.

Significance: Our study shows complex NLR relationships that may be relevant to TBI pathophysiology; hopefully this will give insight to NLR's clinical applicability in risk assessment and prognostication for TBI.

Abstract 42

LONGITUDINAL CHARACTERIZATION OF BIOKINETIC AND CLINICAL ASSOCIATIONS WITH CEREBROSPINAL FLUID AND SERUM T-TAU AND P-TAU FOLLOWING TRAUMATIC BRAIN INJURY: A CONSORTIUM STUDY

Shanley L[1] & Vaughan L,[1] Yang Z,[2] Xu H,[2] Chang B,[3] Barton D,[1] Trifilio E,[2] Williamson J,[2] Wang K,[2] Robertson C,[4] Rubenstein R,[3] Wagner A[1]

[1]University of Pittsburgh
[2]University of Florida
[3]State University of New York-Downstate Medical Center
[4]Baylor College of Medicine

Introduction: A progressive injury response is initiated by traumatic brain injury (TBI) leading to signaling derangements that span the acute to chronic phases of recovery. Tau pathology is implicated in neurodegeneration; however, the mechanistic underpinnings of tau phosphorylation post-TBI remain unclear.

Hypothesis: CSF and serum total (T)-tau, phosphorylated (P)-tau, and P-tau/T-Tau ratio are hypothesized to be viable clinical readouts of tau pathology post-TBI with serum expression extending into the chronic phase and likely impacting recovery.

Methods: Serial serum and CSF samples were obtained from n=244 University of Pittsburgh (PITT) and n=115 Baylor College of Medicine (BC) individuals with moderate-to-severe TBI and measured for tau proteins using RCA-SOFIA platform. Day-0-6 means were used for analysis of both cohorts and additionally Month-1-6 means for PITT serum. Biokinetic and group-based trajectory analyses were implemented to describe serum temporal patterns. Tau protein proteins were assessed with respect to demographic, clinical, and outcome measures including Disability Rating Scale (DRS) and Glasgow Outcome Scale-Extended (GOS-E) scores at 6-months post-TBI in both cohorts, with additional outcome assessment for PITT at 12-months.

Results: In both cohorts, serum T-tau and P-tau are elevated Day-1 and peaked by Day-10. PITT data demonstrated that T-tau and P-tau reach maximum levels at Day-4.4 and Day-4.7, respectively, and exhibit relatively long serum half-lives (65.4 and 37.1 days, respectively). Day-0-6 serum tau proteins were not associated with demographic, clinical, and outcome metrics in either cohort. Among PITT participants, Month-1-6 P-tau and P-tau/T-tau ratio were negatively correlated with GOS-E and positively correlated with DRS at 6- and 12-months post-TBI (higher P-tau, P-tau/T-tau=worse outcome). CSF relationships to outcome were absent in the PITT cohort. However, among BC participants, Day-0-6 CSF T-tau and P-tau were correlated with worse 6-month DRS and GOS-E scores. Both longitudinal (acute vs. chronic) and compartmental (serum vs. CSF) correlations were most evident between P-tau and the P-tau/T-tau ratio.

Conclusions: Day-0-6 CSF and Month-1-6 serum tau protein expression are the main drivers of post-TBI outcome, while Day-0-6 serum associations are not evident in either cohort.

Significance: These findings suggest evidence of tau pathology beyond the initial TBI which manifest in the periphery beyond the acute phase post-injury and contribute to worse global recovery trajectories.

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