22nd Annual

SAFAR SYMPOSIUM

May 15th, 2025

ABSTRACTS

Multi-Departmental Trainees' Research Day

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DEPARTMENT OF ANESTHESIOLOGY AND PERIOPERATIVE MEDICINE

Abstract 1

RETROSPECTIVE ANALYSIS OF EPIDURAL CATHETER IMPACT ON POST-SURGICAL EXTUBATION, OPIOD USE, PAIN, AND SEDATION SCORES IN NEONATAL INTENSIVE CARE UNIT INFANTS

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Introduction: Perioperative pain management is essential for improving outcomes in Neonatal Intensive Care Unit (NICU) infants. Continuous epidural analgesia can facilitate early extubation and improve the infants' outcomes after the surgery. This study investigates the relationship between epidural analgesia, extubation, and key clinical outcomes that could influence extubation and reintubation, such as surgical procedures, demographics, and opioid administration.

Methods: A retrospective chart review was conducted at the UPMC Children's Hospital of Pittsburgh to identify all infants who received an epidural catheter between 2018 and 2024 and required postsurgical admission to the NICU. The study examined the timing of extubation and reintubation along with associated factors in 100 infants who underwent significant surgeries.

Results: One hundred infants, 43 females and 57 males, 40(38.39-42.07) weeks corrected gestational age, 3(2.52-3.42) kg received epidural catheters. Sixty-two patients had a pulmonary condition. Of 45 infants extubated in the operating room, 32 received fentanyl intraoperatively, and 16 required morphine infusion in the NICU. Among 55 infants that remained intubated, 24% underwent a thoracic procedure, 46 received intraoperatively fentanyl, and 21 needed opioid infusion postoperatively. The extubation day was median (IQR) 2(1-4), and 24% remained intubated beyond day 5. Twelve infants were intubated before presenting to surgeries, and six required prolonged ventilation beyond day 5. Of 15 infants that required reintubation, 8 received morphine infusion. The median (IQR) of the average of three pain and sedation scores before reintubation were 1.67 (1 - 3) and 0 (-1.67 - 0), respectively.

Conclusions: Epidural analgesia may facilitate early extubation in some infants undergoing surgeries. Morphine infusion was administered at similar rates between infants extubated and those who remained intubated, and its role in delaying extubation timing remains unclear.

Significance: This study's findings have important implications for clinical practice. They suggest that continuous epidural analgesia may support early extubation in neonatal surgical patients, potentially reducing prolonged mechanical ventilation and its associated risks. These results contribute to the growing body of evidence guiding perioperative pain management strategies in NICU infants and highlight the need for further research on optimizing opioid use.

Research/Grant Support: None

Abstract 2

ANDROGENS MAINTAIN PROTEIN KINASE A SIGNALING OF CHRONIC POSTSURGICAL PAIN SENSITIZATION

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Introduction: Plantar incision leads to the sensitization of spinal neurons (central sensitization) that contributes to acute postsurgical pain. This can be followed by latent sensitization (LS), a long-lasting form of central sensitization that is thought to increase vulnerability for the development of chronic postsurgical pain (CPSP). LS is tonically opposed by opioid receptor activity and can be revealed as a reinstatement of pain-like behavior (e.g., hypersensitivity to mechanical stimulation at the paw) upon the administration of a kappa opioid receptor (KOR) antagonist. LS is maintained by complex intracellular signaling pathways leading to the release of cAMP to engage cAMP receptors, including protein kinase A (PKA). For example, we reported that intrathecal administration of the PKA inhibitor H89 prevented KOR antagonist-induced reinstatement of mechanical hypersensitivity, suggesting a contribution of PKA signaling to LS. Remarkably, H89 was only effective in male mice (Basu et al., 2021), leading us to explore the overall hypothesis that signaling pathways of LS are different between sexes.

Hypothesis: Androgens and androgen receptors maintain the contribution of PKA to CPSP.

Methods: In C57BL/6 male and female mice (7-8 wk), we incised the skin and underlying plantaris muscle at the left hind paw and at 3 wk for hypersensitivity (von Frey filaments) to resolve. On day 21, **1)** in female mice, we administered testosterone enanthate (TE, 0.45 mg/kg, subcutaneous) or vehicle (sesame oil) for two weeks; **2)** in female mice, we spinally administered TE (10 µg, intrathecal) or vehicle (cremophore: ethanol: saline – 1:1:8) ; **3)** in male mice, we administered flutamide (50 mg/kg, subcutaneous) to block AR; **4)** male mice received orchiectomy (surgical removal of testes) or sham surgery (n = 6-8). After each intervention, we administered vehicle, H89 (10 nmol, i.t.), and/or KOR antagonist LY2456302 (10 µg, i.t.) in a 2x2 design in both male and female mice.

Results: LY2456302 reinstated mechanical hypersensitivity in all four experiments as expected. As expected, neither the vehicle nor H89 alone changed mechanical threshold in any expt. Also, as expected, H89 blocked LY reinstatement in male but not female mice. In male mice, pharmacological blockade of AR with flutamide but not the vehicle, as well as orchiectomy (removal of testes) but not sham surgery, reversed the ability of H89 to block pain reinstatement, suggesting that. Conversely, in female mice, systemic or intrathecal testosterone enanthate but not vehicle recruited the ability of PKA inhibitor H89 to prevent reinstatement, suggesting that exogenous testosterone activates the PKA signaling component in females.

Conclusions: We conclude that testosterone-mediated activation of ARs maintains the PKA component of LS in males. Further studies are needed to determine the PKA-independent signaling mechanisms that drive LS in females.

Significance: These data promote PKA and AR inhibitors as novel analgesics for CPSP.

Research/Grant Support: National Institutes of Health grant numbers R01DA37621, R01NS45954, and R01NS62306 to BKT. UPSOM Seed Award, University of Pittsburgh to PB.

Abstract 3

LOCAL AND GLOBAL CHANGES IN FUNCTIONAL MRI CONNECTIVITY WITH INTRAVENOUS LIDOCAINE

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Introduction: Intravenous lidocaine is a commonly used opioid-sparing adjunct medication for perioperative anesthesia, but the neural correlates of its effects during pain are not well understood.

Hypothesis: Intravenous lidocaine affects pain perception and changes brain functional connectivity via local and global circuits.

Methods: Twenty-eight volunteers (14 male, range 20-55 years, mean 31.1 years) completed resting state functional MRI scans under saline and drug conditions in an open-label observational study. Blood oxygen-level dependent weighted (TE=30 ms) images were obtained every 800 ms with 2.1 mm isotropic spatial resolution. Lidocaine dosing began while a high-resolution anatomical image was acquired. Lidocaine was dosed to achieve an effect site concentration of 1.5 mcg/ml using stanpumpR. Once lidocaine reached steady-state, the resting-state fMRI scan was repeated. The connectivity analysis was performed with Conn toolbox using local and global correlation approaches, comparing the lidocaine to no-drug conditions. Local correlations were restricted to within 25 mm of the seed voxel. Group results were thresholded with a voxel-wise threshold of $p < 0.001$ and corrected to an overall false-detection rate of $p<0.05$.

Results: The total dose of lidocaine was 1.8 +/ - 0.1 mg/kg (range 1.7 to 2.0 mg/kg), administered over a mean time period of 27 minutes (range= 21-33 min). The global correlation analysis demonstrated decreased connectivity under the lidocaine condition in seven clusters which included the right lingual gyrus (size= 655 voxels, p-FDR= 0.000114), precuneus (size= 412 voxels, p-FDR= 0.001793), left posterior middle temporal gyrus (size= 280 voxels, p-FDR= 0.010384), and left anterior parahippocampal gyrus (size= 697 voxels, p-FDR= 0.000114). The local correlation analysis showed a decrease in connectivity in the right temporal fusiform cortex (size= 295 voxels, p-FDR= 0.017628).

Conclusions: These results show significantly higher local connectivity compared to global correlations; however, the group-averaged local correlations are unchanged between saline and lidocaine conditions. There is a greater decrease in connectivity under lidocaine compared to saline in global measures of connectivity. Connectivity decreased in regions implicated in visuospatial processing, memory, consciousness, and the default mode network. These results coincide with regions identified in fMRI studies of other anesthetic agents with distinct mechanisms of action.

Significance: Identifying regions implicated in these biologic processes can aid targeted pharmacologic research and clinical practice in the future. Individual variation in response to sedation and analgesia contributes to sub-optimal pain control challenges in managing chronic pain. Identifying more definitive measures of analgesia and anesthesia have important implications for the management of pain in the perioperative setting.

Research/Grant Support: NIH grant R35GM146822

Abstract 4

CHEMOGENETIC ACTIVATION OF MU OPIOID RECEPTOR EXPRESSING NEURONS IN DORSAL HORN BUT NOT ROSTROVENTRAL MEDULLA ELICITS NOCICEPTION

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Introduction: The mu opioid receptor (MOR) is expressed throughout many pain regulatory regions of the central nervous system, including the dorsal horn of the spinal cord (DH) and the rostroventral medulla (RVM). Opioid ligand-induced activation of MOR at these sites exerts potent analgesia. However, the function of the neurons that express MOR in chronic pain is unclear.

Hypothesis: Pharmacological agonism at excitatory neurons that express a neurotransmitter receptor coupled to inhibitory G-proteins ($G_{i/o}$) should reduce pronociceptive signaling. Since MOR agonists produce analgesia, and MOR receptors are coupled to $G_{i/o}$, we hypothesized that *Oprm1*^{Cre}-expressing neurons in the DH and RVM are sufficient for the behavioral manifestations of pain.

Methods: We used a chemogenetics approach to increase the activity of MOR-expressing neurons in the DH or RVM, and a behavioral approach to evaluate sensory and motor function. We injected AAV8-hSyn-hM3D$_{Gq}$ [excitatory designer receptor exclusively activated by designer drug (DREADD) virus] or AAV8-hSyn-mCherry (control virus) into the left lumbar L4 dorsal horn or the RVM of *Oprm1*^{Cre} mice, waited three weeks, induced chemogenetic activation with clozapine-N-oxide (CNO, 3mg/kg, i.p.), and then evaluated behavioral withdrawal responses to mechanical (von Frey), cold (acetone), and heat (hotplate) stimuli. We also determined performance on an accelerating rotarod as a test of motor coordination.

Results: We found that chemogenetic activation of spinal *Oprm1*^{Cre} neurons induced mechanical and cold hypersensitivity but not heat hypersensitivity. Mechanical thresholds at 60 minutes were 1.1 ± 0.5 and 3.2 ± 0.4 grams after CNO and saline, respectively. Withdrawal duration in response to cold stimuli at 120 minutes were 7.1 ± 3.3 and 1.7 ± 0.4 seconds after CNO and saline, respectively. We observed no changes in motor coordination. Surprisingly, chemogenetic activation of RVM *Oprm1*^{Cre} neurons did not elicit any behavioral sign of pain.

Conclusions: *Oprm1*^{Cre} neurons in the DH but not RVM are sufficient for the behavioral manifestations of pain (mechanical and cold hypersensitivity), and thus represent a promising target for the development of new approaches to treat pain.

Significance: A better understanding of the physiology, pharmacology, and circuitry of MOR-expressing neurons in the dorsal horn could lead to the development of safer and more effective approaches to treat acute and chronic pain. Future studies will determine whether chemogenetic inhibition of *Oprm1*^{Cre} neurons in the DH or RVM alleviate pain hypersensitivity following inflammation or nerve injury.

Research/Grant Support: NIH R01DA37621, R01NS45954 and The Raymond and Elizabeth Bloch Educational and Charitable Foundation (PI: Bradley Taylor, PhD)

Abstract 5

INTERACTIONS BETWEEN MAST CELLS EXPRESSING VEGF AND PEPTIDERGIC PRIMARY AFFERENTS MEDIATE PELVIC TACTILE ALLODYNIA IN ENDOMETRIOSIS- AND UTERINE VEGF-ASSOCIATED MOUSE MODELS OF CHRONIC PELVIC PAIN

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Introduction: Endometriosis (EM) globally impacts roughly 10% of women of reproductive age. EM lesions are infiltrated with mast cells (MCs), contain elevated levels of vascular endothelial growth factor (VEGF), and are densely innervated. However, whether neuroimmune interactions exist between MCs expressing VEGF and primary afferent neurons that drive endometriosis-associated chronic pelvic pain (EM-CPP) is unclear. To address this gap, we use a validated EM mouse model that develops pelvic pain originating from the uterus and referred pain from the abdominopelvic muscles. This referred pain can be measured non-invasively in rodent models of EM and is called pelvic tactile allodynia. We use this EM mouse model to reveal that interactions between MCs, VEGF, and primary afferent neurons drive pelvic tactile allodynia.

Hypothesis: In the uterine tissue of mice with pelvic tactile allodynia, MCs expressing VEGF increase near peptidergic primary afferents, but ablation of transient receptor potential vanilloid 1 (TRPV1)-positive primary afferent neurons or neutralization of MC-derived VEGF signaling decreases pelvic tactile allodynia.

Methods: C57BL/6J donor mice (6 weeks old) received a subcutaneous injection of estradiol benzoate (10µg), and 4 days later, each uterine horn was excised and placed in Hank's Balanced Salt Solution (HBSS) and minced. Recipient mice received an intraperitoneal injection of either HBSS (500µl; "Shams") or HBSS+ donor mice minced uterine horn (500µl; "EM mice"). To assess the development of pelvic tactile allodynia, recipient/EM mice calibrated von Frey (vF) filaments were applied to the pelvic region using the up-down method.

Results: Our data revealed that MCs expressing VEGF are adjacent to calcitonin gene-related peptide (CGRP)+ afferents in the uterine tissue of EM mice but not in Sham controls. Next, we assess changes to mechanical withdrawal thresholds in Sham or EM mice after intrathecal (i.t.) injections of either vehicle, capsaicin (CAP; 1µg), or resiniferatoxin (RTX; 25ng). In Shams, neither vehicle, CAP, nor RTX changed mechanical withdrawal thresholds. In EM mice, CAP or RTX but not vehicle reversed pelvic tactile allodynia ($p<0.05$). Follow-up studies demonstrated that intrauterine (i.u.) VEGF dose-dependently induced pelvic tactile allodynia in non-EM mice; thus, we investigated the effect of afferent ablation in this model. RTX but not vehicle reversed VEGF-induced pelvic tactile allodynia ($p<0.05$). In a separate study, we tested the impact of a VEGF-neutralizing antibody on VEGF-induced pelvic tactile allodynia. We i.u. infused saline or VEGF (1pg) and then i.u. infused IgG control or anti-VEGF (1mg/kg). Data revealed that mechanical withdrawal thresholds remain unchanged in controls. However, i.u. anti-VEGF but not i.u. IgG reversed VEGF-induced pelvic tactile allodynia after 9 hours ($p<0.05$).

Conclusions: 1) MCs expressing VEGF are adjacent to peptidergic afferents in EM mice, 2) ablation of TRPV1-expressing primary afferent neurons blunts pelvic tactile allodynia in EM and i.u. VEGF mouse models, and 3) treatment with a VEGF-neutralizing antibody attenuates pelvic tactile allodynia.

Significance: Targeting neuroimmune interactions between MCs expressing VEGF and TRPV1-positive primary afferents is a potential therapeutic method to alleviate EM-CPP.

Research/Grant Support: NIDDK K01DK114395-06 (PI: Kenny Roman, PhD), Competitive Medical Research Fund (PI: Kenny Roman, PhD), and the University of Pittsburgh Start-Up funds (PI: Kenny Roman, PhD, and Co-PI: Bradley K. Taylor, PhD)

Abstract 6

MECHANISMS OF ALCOHOL WITHDRAWAL-INDUCED PAIN: INSIGHTS INTO CHRONIC PAIN VULNERABILITY

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Introduction: Individuals with chronic pain have increased risk of developing alcohol use disorder (AUD), while chronic alcohol use can lead to enhancement of pain sensitivity. This reciprocal relationship causes difficulties in the treatment of AUD as well as inpatient pain management of patients with AUD. Mechanisms underlying pain sensitization are currently unclear and developing understanding will be essential for improving treatment for this patient population.

Hypothesis: We hypothesize that this sensitization occurs in part through activation and prolonged enhancement of neuronal activity in the parabrachial nucleus (PBN), a brain region thought to be involved in the gating and relay of incoming pain signals and their integration with other competing need states. We hypothesize that in an ethanol-withdrawal mouse model we will see enhanced activity of neurons in the PBN when compared to controls.

Methods: We utilized an advanced electrophysiological technique called whole-cell patch clamp to measure the excitability of neurons in brain slices spanning the lateral aspect of the PBN. We evaluated passive and active membrane properties in a chronic intermitted ethanol vapor (CIEV) mouse model of chronic alcohol exposure as compared to their air controls.

Results: Preliminary data demonstrates increased excitation, intrinsic excitability, and decreased inhibitory signaling within PBN neurons in alcohol-treated animals as compared to controls.

Conclusions: Interpretation of the study is limited by low numbers, however data indicates enhanced activity in the lateral PBN in ethanol-treated animals as compared to controls. This data, coupled with prior studies, aligns with our hypothesis and is encouraging for future work.

Significance: Chronic alcohol use may enhance pain sensitivity via central mechanisms such as hyperexcitability of the PBN. Further understanding of this process could lead to enhanced treatment of AUD as well as pain management in individuals with AUD.

Research/Grant Support: R01NS45954 and R01NS112632 to BKT; F31AA31431 to AJB; and a grant from the Pittsburgh Foundation to SF and BKT.

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Abstract 7

APPLYING VIRTUAL REALITY TO MEDICAL EDUCATION: THE FEASIBILITY OF USING VIRTUAL REALITY SIMULATIONS FOR TEACHING CENTRAL VENOUS CATHETER PLACEMENT

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Introduction: The goal of this study was to evaluate the attitudes of medical students towards a virtual-reality (VR) module for teaching central venous catheter (CVC) placement. Specifically, this study sought to determine if the technology was intuitive and accessible, and if students thought the module improved their understanding of the steps required for CVC placement.

Hypothesis: Senior medical students will find that the VR module improves their understanding of the CVC procedure. They will find it intuitive and without major side effects.

Methods: 10 medical students were included, five were randomized to the standard curriculum, which included written instructions and a video. The VR group received the same education with an additional VR module. Students were assessed on CVC placement on a trainer by an observer who recorded the time, number of attempts, and which of the 14 steps were performed. The VR group was assessed on the trainer before and after completing the module. The standard group was assessed only once and was allowed to practice on a trainer and review didactic material while the VR group completed the module. All students completed a pre-study survey that collected demographic data and other variables, including prior experience with CVC placement or VR technology. A post-study survey inquired about disequilibrium effects, procedural confidence, and system usability, among other subjective outcomes. Between group comparisons were done with an unpaired t-test or ANOVA, while comparisons of the pre- and post-VR module assessments were done with a paired t-test.

Results: There were no differences among measures of success of CVC placement including time to completion or number of attempts. The performance of participants in the VR group did not differ from pre- and post-completion of the VR module. Importantly, when students had the opportunity to rate the ease of use of their instructional system, students in the VR group found it easier to use ($p=0.0008$). Further, students in both groups rated their procedural confidence higher on the post-survey ($p=0.0007$, $p<0.0001$). Both the mannequin and the VR headset were evaluated with the system usability scale (SUS). The VR headset scored 78.0, while the mannequin scored 54.5, and this difference was statistically significant ($p=0.0146$). Importantly, no participants experienced any side effects.

Conclusions: Students found that using a virtual reality headset to learn CVC placement was easy to use, free of side-effects, and significantly increased their confidence with the procedure.

Significance: VR modules will improve skills training at the medical student level. They can easily be implemented into current curriculums and are favorably received by students.

Research Support: Academy of Distinguished Medical Educator Scholarship: Innovations in Medical Education/UPMC Department of Anesthesiology & Perioperative Medicine: Educational Seed Grant, UPMC Mercy Hospital/Vantari VR, Seattle Washington.

Abstract 8

SMART CUFF FOR MULTI-PARAMETER HEMODYNAMIC MONITORING: AN INITIAL NON-INVASIVE APPROACH TO CARDIAC OUTPUT TREND ESTIMATION

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Introduction: Monitoring cardiac output (CO) and blood pressure (BP) is essential in surgical and intensive care units as indicators of hemodynamic instability, guiding precise treatment and medical interventions, such as fluid administration and vasopressor therapy. However, current monitoring methods require multiple devices that are invasive, operator-dependent, or require specialized tools. These challenges highlight the need for a non-invasive, reliable tool for monitoring CO trends and BP. *Hypothesis*: A non-invasive estimation of CO trends can be achieved by analyzing cuff-derived pressure waveforms. Specifically, the product of the maximum peak-to-peak amplitude of the cuff pressure oscillation ($Pacmax$) and heart rate (HR) can be used to estimate CO trends, with predicted values compared to the trend of thermodilution CO measurements.

Methods: *Device:* A custom cuff device was developed with a linear deflation-based function. The device rapidly inflates the cuff until arterial occlusion and then slowly deflates while measuring cuff pressure. *Data Collection:* The custom cuff device was used in operating rooms (ORs) and intensive care units (ICUs) on a total of 24 patients undergoing cardiac, liver, or lung procedures. A few cuff inflation-deflation pressure measurements were collected from each patient at the time of bolus administration for recording CO thermodilution measurements, along with all bedside monitor data. Patient demographics were also recorded. *Data Analysis:* Each cuff pressure deflation waveform was filtered using a bandpass filter with frequencies ranging from 0.5 Hz to 5 Hz to extract cuff pressure oscillations. The maximum peak-to-peak amplitude ($Pacmax$) was then extracted from these oscillations, along with heart rate (HR).

Results: The change in the cuff-based feature ($\Delta Pacmax * HR$ %) showed a concordance rate of 73% with respect to changes in thermodilution CO (ΔCO %). Comparatively, a well-established CO estimation method, $\Delta PP/(ISP + IDP) * HR$%, showed an 86% concordance with ΔCO%. Moreover, the correlation between $Pacmax * HR$ and absolute thermodilution CO was 0.63. Additionally, when considering anthropometric factors such as body mass index (BMI), the correlation between $BMI{*}Pacmax * HR$ and CO increased to 0.68.

Conclusions: An arm cuff-based method can potentially be developed to detect CO trends by estimating changes in blood volume through the brachial artery. Incorporating anthropometric factors may improve trend prediction. Furthermore, the cuff-based method has the potential to be refined for estimating absolute CO values.

Significance: A simple, automated arm cuff device could be used to detect changes in CO, thereby indicating hemodynamic instability. This method would enable clinicians to make precise treatment decisions while reducing medical costs.

Research/Grant Support: This work was supported by the NIH Grant HL163691.

Abstract 9

GLOBAL KNOCKOUT OF GLYCINE RECEPTOR α3 HINDERS RECOVERY FROM POSTOPERATIVE PAIN

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Introduction: Acute postoperative (PO) pain is a common clinical complication which usually resolves within 7-10 days. For reasons yet unknown, >3-10% patients experience "chronification" of PO pain for ≥3 months or even permanently. Understanding the mechanisms of acute-to-chronic pain transition is imperative to alleviating symptoms and helping patients return to normal living. Glycine receptors, specifically glycine receptor α3 (GlyRα3), are known to play a major role in pain signaling. Here we use global GlyRα3 knockout (KO) mice derived from C57BL/6J mice to determine GlyRα3's role in recovery from PO pain.

Hypothesis: We hypothesize that with reduced inhibitory control, GlyRα3 KO mice will take longer to recover from PO pain.

Methods: We evaluated the pain behavior of 32 female mice, 16 wild type C57BL/6J (WT) and 16 GlyRα3 KO mice. Animals were further divided into two groups for acute and chronic PO pain models. Three behavioral measures, Von Frey, Hargreaves, and thermal gradient tests (TGT), were used. The plantar incision model, in which a small incision is made on the left hind paw, was performed for acute PO pain. For chronic PO pain, the skin and muscle of the left thigh were incised and opened with a retractor for 1 h to simulate a clinical procedure. The skin of the right thigh was incised and sutured as a sham procedure.

Results: In the acute phase of the plantar incision model, direct noxious stimulations administered at the surgical wound by the Hargreaves and von Frey tests showed hypersensitivity but could not differentiate the WT and KO groups. The new TGT for a self-reported comfortable range of temperatures after plantar incision, in contrast, separated KO from WT mice: the incision caused persistent "cold-shifts" for more than 37 days in the KO mice while WT mice recovered in 7-9 days. In the chronic model, mechanical hypersensitivity could be detected by the von Frey test on the hind paw of the surgery side. Again, GlyRα3 KO mice showed significantly slower recovery (18 days in WT vs. 31 days in KO), suggesting the involvement of GlyRα3 in chronic inhibition and final resolution of pain in the WT mice.

Conclusions: Behavioral data suggest that GlyRα3 plays a critical role not only in the sensitization of pain, but also in the recovery and resolution from pain. The mechanisms by which GlyRα3 aids in the chronification of, and recovery from, painful conditions warrant further study.

Significance: These new findings are key to understanding the recovery process from PO pain and will aid in the discovery of new molecular targets for drug development to control and prevent chronification of PO pain.

Research Grant Support: This work is supported in part by R01NS122830 to YX

Abstract 10

PATIENT CONTROLLED OPIOID-FREE SURGICAL PROGRAM

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Introduction: Increasing numbers of patients are now requesting non-opioid surgeries. Mousad et al [1] and Schneider et al. [2] demonstrated that multimodal pain management, including regional anesthesia, achieves opioid free surgery in only 50% of cases. To increase success rates for patients requesting opioid free surgery, we developed the Patient-Driven Opioid-Free Surgical Pathway (PDOFSP). This program is based on education, increased communication, and tailored use of complementary techniques—like aromatherapy [3], mindful breathing, RxWell (a mobile cognitive-behavioral app) [4], auriculotherapy [5], hypnosis, nanotechnology [4], acupuncture, and music therapy [6]—to control both physical and psychological factors of surgical pain. Recent work by Patsalis et al. suggests that combining multiple complementary techniques may have synergistic effects [7].

Hypothesis: A patient-centered pathway that integrates techniques to manage both physical and psychological aspects of pain can maximize the number of patients who successfully undergo opioid-free surgery, specifically those who refuse opioids.

Methods: First, patients join the pathway by request or after the acute pain nurse practitioner (NP) assesses their opioid preferences. Second, once identified, patients are educated on our program and develop an individualized pain plan based on the use of non-opioid drugs, regional anesthesia, and complementary techniques applied prior to surgery. On surgery day, a wristband and chart sticker indicate the patient's opioid-free preference, and a special-order set ensures appropriate non-opioid pain control. The last component of the program includes a close follow up by our NP.

Results: Our preliminary results highlight the potential of the PDOFSP used across broad surgeries: 73% didn't receive any opioids (127 of 173 patients). Among the patients who received opioids 1% (2 patients) received opioids during surgery, 17% (30 patients) received opioids in the recovery room and 8% (14 patients) requested to be withdrawn from the PDOFSP. The average length of stay for patients in the PDOFSP was 1.50 days. Notably, 5 patients requested to re-enroll in the PDOFSP for a subsequent surgery, indicating both satisfaction with the pathway and confidence in its effectiveness.

Conclusions: These findings support the PDOFSP as a safe and effective alternative to satisfy a patient's request for opioid free surgery. Improving the selection process, enhancing education for both patients and staff, regularly updating available complementary techniques, and continuously monitoring outcomes are key to increasing our current success rate.

Significance: The significance of patient-directed opioid-free surgery lies in its ability to enhance patient autonomy and expand treatment choices, ultimately promoting greater satisfaction and improved outcomes. PDOFSP represents a much-needed program.

Research/Grant Support: UPMC Shadyside Hospital Foundation, Beckwith Institute, NIH-R21DA061414

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Abstract 11

USE OF TAMOXIFEN WHEN STUDYING ETHANOL CONSUMPTION AND PREFERENCE FOR C57BL/6J MICE

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Introduction: Tamoxifen (TAM) inducible Cre/loxP mice are one of the most commonly used systems for temporal control over gene expression *in vivo*. However, mon-selective effects of TAM may impact interpretation of behavioral studies, including studies of ethanol consumption and preference.

Hypothesis: TAM drives behavioral changes in ethanol consumption.

Methods: We conducted a series of studies to investigate potential effects of TAM on ethanol drinking behavior of mice on a C57BL/6J (B6J) genetic background. Male and female 5-week-old B6J mice received either TAM (150 mg/kg, *i.p.*) or corn oil vehicle control for five consecutive days. Following 10 days of recovery B6J mice underwent the every-other-day two-bottle choice (EOD-2BC) or chronic intermittent ethanol vapor exposure 2BC (CIEV-2BC) paradigm to model non-dependent and dependent drinking, respectively. Follow-up EOD-2BC experiments allowed 24 days of recovery from TAM. We validated our findings using data from collaborators, who tracked weight as well as changes in ethanol drinking using the drinking-in-the-dark (DID) model.

Results: 10 days of TAM recovery led to a female-selective decrease in ethanol consumption and preference in EOD-2BC. Male and female CIEV-2BC mice demonstrated an initial decrease in ethanol consumption and preference during the first 2-weeks of testing but returned to vehicle control levels. Follow-up EOD-2BC experiments after 24 days of recovery from TAM injections showed no significant differences in ethanol consumption behavior compared to corn oil controls. Female B6J mice given five days of TAM (75 mg/kg, *i.p.*) also showed no differences in the DID model. In another experiment, 7-week-old mice received TAM (75 mg/kg, *i.p.*) or corn oil vehicle for five consecutive days. Tamoxifen-treated males and females showed a significant decrease in body weight over the treatment period, but weight gain matched that of corn-oil controls by one-week post-treatment and did not differ from corn-oil controls over three weeks of post-treatment monitoring. TAM (150 mg/kg, *i.p.*) treatment caused a significant decrease in male and female B6J mice throughout multiple weeks of the nine-week testing period, suggesting a general TAM-induced sickness response that was longer lasting in female mice.

Conclusions: Our studies highlight potential confounding effects of TAM in ethanol behavioral research, which can vary by dose, recovery time, and biological sex.

Significance: Properly accounting for tamoxifen's impact is essential for reliable interpretation of gene function in preclinical models of ethanol consumption and preference.

Research/Grant Support: We gratefully acknowledge the support of the INIA-Neuroimmune consortium and NIH/NIAAA funding F31AA032172, U01AA020912, U01AA016651, U01AA020889, R01AA030257.

Abstract 12

LOSS OF NEURONAL MD-1 EXPRESSION LEADS TO INCREASED INFLAMMATION IN AN IMIQUIMOD-INDUCED MODEL OF PSORIASIS

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Introduction: The immune response to cutaneous insults requires the interaction of many cell types, including immune cells, keratinocytes and sensory neurons. While the role of peptidergic sensory afferents, which release neuropeptides like CGRP and Substance P, has been well studied, the role of nonpeptidergic sensory afferents that contain a limited quantity of neuropeptides remains elusive. In a recent study, Mrgprd-expressing nonpeptidergic neurons have been shown to suppress mast cell activation, suggesting an immune suppressor function. Transcriptomic studies of sensory neurons show that myeloid differentiation 1 (MD-1), a molecule associated with the innate immune response, is produced almost exclusively by Mrgprd-expressing sensory neurons. Studies of MD-1 demonstrate that decreased MD-1 mRNA expression is associated with proinflammatory disorders, such as lupus and obesity, suggesting an anti-inflammatory function. Interestingly, neuronal MD-1 expression increases in the presence of neurturin (NRTN), a member of the glial cell line-derived neurotrophic factor family. NRTN supports nonpeptidergic neuron development and is implicated in the skin pathogenesis of the murine imiquimod (IMQ) model of psoriasis. Therefore, this model was selected to investigate the role of neuronally expressed MD-1 in the cutaneous immune response.

Hypothesis: Loss of neuronal MD-1 expression in nonpeptidergic neurons leads to increased inflammation and a sustained immune response in an IMQ-induced model of psoriasis.

Methods: IMQ was applied daily to the ear or dorsal skin of MrgprDcre *Ly86-/-* conditional knockout mice (CKO) as well as wild-type littermate controls (WT) for 6 days. Over the course of treatment, dorsal skin was evaluated for the level of inflammation using the psoriasis area and severity index (PASI) score and ear skin inflammation (edema) was evaluated using a micrometer. mRNA expression of select immune and inflammatory cytokine markers in the dorsal root ganglia (DRG) and skin was evaluated. DRG cells were also assessed for cell viability in the presence of IMQ using fluorometric assays.

Results: A lack of neuronal MD-1 expression resulted in elevated PASI scores, ear swelling, and mRNAs encoding *Ly6G* (a marker of neutrophil cells) in the skin. The level of IL-1β (a proinflammatory cytokine) mRNA in the DRG of CKO relative to WT mice was also increased.

Conclusions: Loss of neuronal MD-1 expression leads to a sustained neuroimmune response. This suggests a role for MD-1 in the response to and resolution of inflammatory challenges.

Significance: This study provides insight into the role of nonpeptidergic afferents in the cutaneous immune response and may lead to adjunctive approaches to treat inflammation.

Research/Grant Support: Support was provided by UPP Foundation Research Grant (MRJ), VA VISN4 Competitive Career Development Fund (MRJ), and NIH Grant #NS033730 (KMA).

Abstract 13

EFFECTS OF PULSED TRANSCRANIAL ELECTRICAL STIMULATION (pTES) ON FIBROMYALGIA (FM) PAIN: A CASE STUDY IN TWO PARTICIPANTS

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Introduction: Fibromyalgia (FM) is a serious chronic pain condition that affects millions of people in the US alone. While medications are commonly prescribed to manage FM pain, other neuromodulation methods, such as transcranial magnetic stimulation (TMS), are also explored as potential treatment methods. Among such is pulsed transcranial electrical stimulation (pTES), a non-invasive neuromodulation technique that can directly activate cortical neurons. In this study, we investigated the effects of daily sessions of pTES over the primary motor cortex (M1) of the arm and leg somatotopy on two participants with FM.

Hypothesis: We hypothesize that pTES of M1 will reduce FM pain and that targeting the M1 somatotopy of the region of worst pain will have an added effect.

Methods: We recruited two participants (Fib01 and Fib02) with FM from the local community, who provided written informed consent. We placed 10mm gold cup electrodes on the optimal scalp locations for evoking motor responses in the upper and lower limbs. To monitor motor responses, we placed electromyography (EMG) sensors on the dominant upper limb (hand, lower and upper arm), and bilaterally on tibialis anterior, gastrocnemius, and feet. Both participants visited the lab over several weeks, during which we delivered 1000 pulses of TES per session at motor threshold over the arm and leg somatotopic M1 areas. Daily changes in pain, other FM symptoms, and quality of life were measured by the Revised Fibromyalgia Impact Questionnaire (FIQR) and with voice recordings of qualitative descriptions from the participants. Participants were instructed to weigh the past 24 hours more heavily in their response to FIQR questions.

Results: Utilizing various techniques to reduce scalp pain caused by pTES developed in our lab, we were not only able to elicit clear motor responses in the target muscle groups, but also perform multiple weeks of 4-5 sessions per week, while keeping the scalp pain caused by pTES below 6 on a numeric rating scale of 0-10. Fib01, who reported their region of worst pain to be the lower limbs, showed a 42.2 point decrease in pre-session FIQR score after 4 successive sessions of leg stimulation, from 61 to 18.8, which is within the healthy control group range (Bennet et al., 2009), as well as striking improvements on their self-reported quality of life. On the other hand, after 4 successive sessions of arm stimulation, the FIQR increased by 22.7 points. On Fib02, the FIQR score was reduced from 35.5 to 8.5 with 13 overall sessions, with no clear difference between weeks of arm and leg stimulation (their region of worst pain being the upper back).

Conclusion: These cases show that daily sessions of M1 pTES can be tolerated by FM patients and can reduce pain caused by FM, thus improving quality of life. Future studies on a larger cohort may corroborate these findings and delineate the difference in arm and leg M1 stimulation, and even uncover the potential of targeting the M1 region of worst pain.

Significance: In patients with refractory FM, non-pharmacological treatment methods, such as pTES, may be promising alternatives for symptom management. This study complements literature evidence from TMS that shows that M1 stimulation eliciting motor responses is related to pain reduction.

Research/Grant Support: Pitt CTSI Women's Pain Research Challenge (PI: Benedict Alter, MD, PhD)

Abstract 14

BLUE LIGHT AS AN ANTI-INFLAMMATORY AND ANALGESIC STRATEGY IN THORACIC TRAUMA (BLAASTT): A PILOT RANDOMIZED CONTROLLED TRIAL IN ADULTS WITH PAINFUL RIB FRACTURES

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Introduction: Blue light has been shown to have immunomodulatory benefits in multiple preclinical studies. *In vivo* pathways involve optic nerve stimulation with transmission to the central nervous system, activation of parasympathetic pathways terminating at the spleen, and reduced downstream inflammatory injury. Blue light's known effects on pain mediators including inflammatory cytokines and autonomic tone suggest that blue light may also have analgesic properties. Thus, we launch a pilot randomized controlled trial (RCT) to demonstrate feasibility and acceptability in adult trauma patients with painful rib fractures prior to recruiting the full cohort required to demonstrate clinically significant analgesia.

Hypothesis: A RCT comparing a blue light intervention to both white light and usual ambient light will be feasible and acceptable in adult trauma inpatients with painful rib fractures.

Methods: Eligible adult (≥18 years) trauma inpatients with painful rib fractures are consented and randomized 1:1:1 among three arms: blue light intervention (peak wavelength 442 nm, ~1400 lux), white light comparison (full spectrum, ~1400 lux), and usual ambient light control. Interventions are administered at bedside for 4 hours daily for up to 3 days using light therapy lamps fitted with appropriate filters and mounted on stands with rolling casters. Across study participation, chest wall pain intensity with deep breathing is elicited using an incentive spirometer and recorded on an 11-point numerical rating scale. Blood samples are collected daily for analysis of inflammatory and circadian biomarkers. Initial enrollment is planned for 1 year (through October 22, 2025) after which progression to an RCT powered to detect a difference in pain control (n = 75) will occur only if the following feasibility and safety criteria are met: total enrollment > 25 participants, retention rate >80%, and no serious safety concerns.

Results: The trial launched on October 23, 2024, and 7 participants have enrolled to date (March 28, 2025). With a recent addition of study team members to maximize recruitment, it is expected that the 1-year enrollment target will be met. No study withdrawals, side effects, or safety concerns have occurred.

Conclusions: Early data suggests that the proposed RCT will be feasible and acceptable in adult trauma patients with painful rib fractures.

Significance: If shown to be effective in the full RCT cohort, blue light will offer a novel nonpharmacologic pain management strategy that is low-risk, low-cost, and likely broadly applicable to human inflammatory pain states.

Research/Grant Support: T32GM075770 (PI: Yan Xu); University of Pittsburgh Department of Anesthesiology & Perioperative Medicine Seed Award; UL1 TR001857 (CTSI)

Abstract 15

IDENTIFYING NEW-ONSET NOCIPLASTIC PAIN IN PATIENTS WITH LOW BACK PAIN

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Introduction: Low back pain (LBP) often has nociceptive and neuropathic components,[1] which are risk factors for the development of nociplastic pain.[2] Nociplastic pain is associated with more widespread pain identified by an increased number of painful regions on a body map.[3]

Hypothesis: We used patient-reported outcomes (PROs) from an observational cohort from the University of Pittsburgh's Patient Outcomes Repository for Treatment registry (PORT) to test the hypothesis that in the course of routine care for low back pain, sensitization leads to more widespread pain, reflecting new onset nociplastic pain.

Methods: The University of Pittsburgh IRB approved this retrospective study with a waiver of individual informed consent. Included patients had selected a low back region as painful on a body map (baseline) and completed a body map after 3 months. Subjects were grouped based on the change in the number of painful regions (NPBR) selected after 3 months: 'Toward Less widespread pain' (≥20% decrease), Minimal change (<20% change), and 'Toward Widespread pain' (≥20% increase). NPBR were compared at baseline and 3 months (repeated measures ANOVA, Bonferroni post-hoc test, $p<0.05$). Baseline mental health, physical function, sleep disturbance, depression, and anxiety were compared amongst groups (ANOVA, $p<0.05$).

Results: 16,345 patients were included. The Toward Widespread pain group showed an increase of 74.5% in NPBR over 3 months ($p<0.001$), likely reflecting nociplastic pain, and the Toward Less widespread pain group showed a decrease of 51.7% ($p<0.001$). Baseline PROMIS measures were associated with increased NPBR, including lower mental health and physical functions scores, and increased sleep disturbance, depression, anxiety ($p<0.05$).

Conclusions: We identified a subset of patients with LBP who may have developed new nociplastic pain over 3 months. Future studies will further investigate these changes.

Significance: Early identification and intervention may improve outcomes for patients with low back pain at higher risk for developing nociplastic pain.

Research/Grant Support: None.

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Abstract 16

CHARACTERIZING INTRA-CARDIAC CONNECTIVITY BEFORE, DURING, AND AFTER ISCHEMIA WITH AN AUTOREGRESSIVE DEEP LEARNING FORECASTING MODEL

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Introduction: Accurately modeling cardiac electro-physiologic activity has long been a goal of the academic community. This is unsurprising: perhaps no other organ's continual activity is so directly and obviously tied to life. Creating a novel predictive model that respects biologic constraints can both elucidate underlying pathophysiology and make clinically valuable predictions. We build a machine learning model which does two tasks: (1) conforms to biophysically interpretable architecture and (2) predicts aberrant pathophysiology and indicates potential areas of intervention.

Hypothesis: By using a machine learning forecasting model which incorporates adjacent nodal activity, we will find differences in graph-summary measures of inter-regional communication among epicardial areas before and after an induced ischemic event due to the ischemic event itself.

Methods: Epicardial recordings from 8 porcine hearts were recorded with a sock of 56 electrodes before and after an induced ischemic event (ligation of the LAD with a surgical suture). Approximately 1 hour of epicardial data was collected before and after this induced ischemia. This data was processed with neurokit2 in Python. The processed data was fed into multivariate long-short term memory networks for every one of the 56 regions; each of which forecasts timeseries evolution 8 timesteps into the future for model regularization. These individual models were then fed into a second layer of predictive model wherein predictions from adjacent regions were used in an ensemble model. Putative inter-regional connection strengths are measured as the weights contributing to the ensemble, and these connections before and after ischemia are analyzed and summarized with the small world index graph summary measure.

Results: The small world indices are as follows: before ischemia: 3.98±0.24, after ischemia: 4.02±0.26, p=0.62.

Conclusions: Ischemic events do not robustly change the global communicability between epicardial regions as measured with the small world index.

Significance: This model represents a unique in-silica experimental platform to characterize physiologic changes after ACS. Determining these behaviors will ultimately allow us to determine specific electrical biomarkers that could be dynamically targeted after an MI. This is another step in the direction of personalized medicine to identify specific targets for pharmacologic, technologic, or surgical intervention.

Research/Grant Support: NSF ACCESS Postdoc Supercomputing Grant MED250003 (Mellema), NIH K08 HL135418 (Howard-Quijano), NIH RO1 HL136836 (Mahajan), NIH R44 DA049630 (Mahajan), UPMC Competitive Medical Research Fund (Salavatian)

Abstract 17

THE INFLUENCE OF PATIENT AGE ON INTRAOPERATIVE BLOOD TRANSFUSION PRACTICES: A RETROSPECTIVE ANALYSIS

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Introduction: Anesthesiology teams transfuse more than 50% of all blood products used at major hospitals. The decision to transfuse is multifactorial and shared between anesthesiology and surgery teams and often considers intraoperative bleeding, hemodynamic stability, and patient comorbidities. However, research has shown that patient demographics unconsciously influence the decision to transfuse, specifically, black patients were found to receive more transfusions intraoperatively compared to whites. Further research is needed to elucidate the potential role of other patient demographics, such as age, in intraoperative blood management.

Hypothesis: Patient age is associated with differences in intraoperative transfusion practices, specifically the likelihood of using blood salvage versus packed red blood cells (PRBCs).

Methods: We conducted a retrospective review of intraoperative records of procedures performed between January 1st, 2013, and December 31st, 2020, at UPMC operating rooms, only including elective non-cardiac surgery adult patients with echocardiogram and ejection fraction (EF) estimate within one year prior to surgery. Data included procedure date, type, and length, patient demographics and comorbidities, and intraoperative transfusions. Patients were classified as primarily transfused with PRBCs or with salvaged blood. Multivariate logistic regression models were built to quantify the role of age as a predictor of transfusion practice.

Results: A total of 6,720 patients met inclusion criteria; most patients underwent orthopedic (22.26%), thoracic (17.92%), and vascular surgery (15.03%). Of those, 5,736 patients (85.36%) were primarily transfused with PRBCs. The proportion of patients mostly transfused with salvaged blood increased over time, 8.83% in 2013 and 20.5% in 2020. In the group mostly transfused PRBCs, median age was 66 years(IQR:56-75), 55.11% were men, 85.62% white, median ASA 4, median Charlson Comorbidity Index(CCI) 2 points(IQR:1-3), median EF 55%(IQR:55-60), median preoperative hemoglobin 8.9(IQR:7.9-10.3), and platelets 220(IQR:148-317.5). Median surgery length 178 minutes(IQR:102-307) and transfused a median of 600 mL (IQR:300-620) of PRBCs. Conversely, among those mostly transfused with salvaged blood, median age was 65 years(IQR:57-73), 65.35% men, 91.16% white, median ASA 3, median CCI 1 point(IQR:0-2), median EF 55%(IQR:55-60), median preoperative hemoglobin was 13.3 (IQR:11.9-14.4), and platelets 206(IQR:158-252). Median surgery length 232 minutes (IQR:151.5-337) and transfused a median of 375 mL(IQR:225-750) of salvaged blood. In the logistic regression model adjusted by confounding variables, patient age showed an odds ratio of 1.011, p-value 0.034. No significant differences were observed with patients' race or sex.

Conclusion: The odds of receiving PRBCs instead of salvaged blood intraoperatively increased by 1.1% for each additional year of patient age, after accounting for significant confounders.

Significance: Improving our understanding of what patient demographic characteristics could influence our decisions regarding intraoperative blood management is imperative, especially when it may lead to unintended differences in treatment.

Research/Grant Support: None.

Abstract 18

COGNITIVE PERFORMANCE AND PAIN PERCEPTION WITH SEVOFLURANE IN HEALTHY ADULTS

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Introduction: Sevoflurane is a commonly used anesthetic agent, but few studies have quantified relative impairment of specific cognitive abilities. This study quantifies the effects of low-dose sevoflurane on memory and pain perception.

Hypothesis: We hypothesize that memory performance and reported pain ratings will be significantly reduced by sevoflurane.

Methods: Behavioral data was collected from adult volunteers aged 18-59 (29.4±11.4yrs, 13M, 7F) in a single-arm, open-label, clinical trial study comparing sevoflurane to no-drug baseline. A sedative dose of sevoflurane, an end-tidal expired concentration of 0.4%, was delivered. An electric nerve stimulator delivered a series of painful electric shocks (set in advance to a current level rated 7/10 intensity) and these were rated for intensity and unpleasantness. An image recognition task, free from shocks, was performed by showing a series of complex geometric colored shapes presented every 15 s. Attention was assessed with a 3-back task, and long-term memory was assessed by identifying new or old shapes presented > 60 s later. A longer memory encoding task was performed in which subjects heard a series of common nouns and were instructed to create a mental picture of the word to encourage memory encoding. One-third of these words were also paired with painful electric shocks. In a next-day follow up session, participants heard all words from the prior day and an equal number of new words; they were tasked with identifying which words were heard the previous day. Performance for all tasks was determined using the signal detection metric d´ and compared between drug and no-drug conditions. Formal statistical analysis has been deferred due to the small sample size of data processed thus far.

Results: Preliminary analysis (n=8) shows d´ averages for the 3-back task at baseline= 0.95 (SD= 0.90) and sevoflurane= -1.48 (SD= 1.14). Average d´ for long-term memory at baseline= 1.42 (SD= 2.07) and sevoflurane= -2.42 (SD= 1.27). Preliminary analysis (n=6) shows d´ averages for the next-day memory were no-drug= 0.84 (SD= 0.74) and sevoflurane= 0.08 (SD= 0.47). Average pain intensity scores at baseline= 6.5 (SD= 0.7) and sevoflurane= 5.7 (SD= 1.3). Average pain unpleasantness scores at baseline= 5.6 (SD= 1.5) and sevoflurane= 5.0 (SD= 1.7).

Conclusions: These interim results suggest that sevoflurane negatively affected attention and memory and was effective at reducing pain perception, both intensity and unpleasantness.

Significance: Clinical assessment of patients under anesthesia is limited. Better quantification of cognitive effects of sevoflurane could help guide anesthetic selection to ensure amnesia and analgesia.

Research/Grant Support: R35GM146822 (PI: Keith Vogt, MD, PhD)

Abstract 19

GREATER OCCIPITAL NERVE BLOCKS AND EPIDURAL BLOOD PATCH FOR TREATING ATYPICAL POST-DURAL PUNCTURE HEADACHE - A CASE REPORT

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Introduction: Postdural puncture headache (PDPH) is a common complication of diagnostic lumbar punctures and neuraxial anesthesia. It is typically positional and may be accompanied by neck stiffness, photophobia, and nausea. PDPH occurs in up to 11% of lumbar punctures, with 90% of cases appearing within 72 hours and most resolving within a week. This report presents an atypical case of PDPH with a delayed and prolonged course.

Case Report: A 13-year-old male with celiac disease presented with fever, altered mental status, and possible seizures. Infectious workup confirmed influenza A. Lumbar puncture ruled out bacterial meningitis, and EEG suggested encephalopathy. Brain MRI showed diffusion restriction in the splenium of the corpus callosum, consistent with viral encephalitis. He was diagnosed with influenza A encephalitis and treated with IV Methylprednisolone and Levetiracetam. After recovery, he was discharged home on day six. Following the lumbar puncture, he experienced mild headaches managed with acetaminophen and ibuprofen. Ten days later, he developed worsening positional headaches with neck stiffness, becoming debilitating by day 16, prompting an emergency department visit. Repeat brain MRI showed mild diffuse dural enhancement. He was admitted and treated with ketorolac and prochlorperazine. Acute Pain Service evaluated for an epidural blood patch. He had persistent positional headaches and limited neck flexion but denied photophobia, tinnitus, or weakness. The differential included migraine, encephalitis sequelae, and postdural puncture headache. Given family preference for conservative treatment, he was started on scheduled acetaminophen, ibuprofen, magnesium oxide, and riboflavin. Caffeine was withheld due to age. An ultrasound-guided bilateral greater occipital nerve block with ropivacaine provided brief relief. The next day, an epidural blood patch was performed under general anesthesia with a laryngeal mask airway. Twelve cc of sterile blood was administered at L3-L4. He remained flat for 4 hours, had complete symptom resolution, and was discharged home.

Discussion/Conclusion: This case highlights an atypical presentation of postdural puncture headache (PDPH). Consultation 16 days post-lumbar puncture is rare, making PDPH a less likely initial diagnosis. MRI did not support chronic PDPH, and the diagnosis was only confirmed after symptom resolution following an epidural blood patch. This case underscores that PDPH can present later and persist longer than expected, with diagnosis primarily based on clinical presentation. While MRI is generally not indicated, findings may include small ventricles, brain sagging, engorged venous sinuses, subdural fluid collections, pituitary enlargement, and diffuse meningeal enhancement. Most PDPH cases resolve with conservative management, including caffeine and simple analgesics. Greater occipital nerve blocks are increasingly used to alleviate nerve irritation from dural stretch, offering a minimally invasive option, especially for children or those hesitant about an epidural blood patch. The transnasal sphenopalatine block is another consideration. However, the epidural blood patch remains the gold standard and definitive treatment for PDPH.

Abstract 20

EVALUATION OF A PRECLINICAL MODEL OF OSTEOARTHRITIS INDUCED BY NALIDIXIC ACID

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Introduction: Osteoarthritis (OA) is a degenerative joint disorder and a leading cause of disability, affecting over 500 million people worldwide. Currently there are no long-term clinical interventions for the treatment of OA, except for artificial joint replacement. The use of preclinical models of OA is, therefore, vital to understanding the development of OA. While existing models offer insights into the progression of OA, a clinically relevant rodent model of OA has yet to emerge.

Hypothesis: We hypothesize that the administration of the antibiotic nalidixic acid near the knee joint of juvenile mice will result in OA later in adult life.

Methods: Juvenile mice, between 1-2 months of age, were injected with nalidixic acid at 100 mg/kg or saline near the knee joint. We tested the animals' gait at approximately 1 year and near 2 years of age using a touchpad protocol developed in our lab. We also collected knee joints for H&E histological evaluation of OA development.

Results: Using scores taken from histological evaluation of OA in the knee joint, we performed the Wilcoxon rank-sum test and found that mice injected with nalidixic acid are significantly different from the saline injected animals ($p<0.05$). We also evaluated the gait of mice using a touchpad and calculated several gait features using customized procedures developed in R. The OA mice demonstrated significant differences in the duration of touch, distance covered between consecutive touches, and distance covered between 1st and 3rd, 1st and 4th , and 1st and 5th steps.

Conclusions: Our histological and touchpad gait assessment data support the notion that injection of nalidixic acid in the knee joint of juvenile mice can lead to changes in the knee joint consistent with OA in later life.

Significance: The present findings provide support for the use of nalidixic acid as a preclinical model for osteoarthritis. Further research will aid in the understanding of the development of OA, leading to the discovery of early diagnostic tools and additional clinical interventions.

Research/Grant Support: This work is supported by R01NS122830 to YX

Abstract 21

LONG NONCODING RNA *GAS5* MODULATION OF ETHANOL-RELATED PHENOTYPES *IN VITRO* AND *IN VIVO*

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Introduction: *Growth arrest specific 5* (*Gas5*) is a long noncoding RNA that represses glucocorticoid receptor (GR) activity and modulates inflammatory and apoptotic pathways. *GAS5* is differentially methylated in the brain of humans with alcohol use disorder (AUD); In mice, *Gas5* overexpression in nucleus accumbens (NAc) decreases cocaine seeking. We previously found in mice: (1) A neuron-specific decrease in *Gas5* expression in male medial prefrontal cortex (mPFC) following chronic intermittent ethanol vapor exposure; (2) A male-specific increase in voluntary, non-dependent ethanol consumption in the two-bottle choice (2BC) paradigm following mPFC neuron *Gas5* knockdown (KD).

Hypothesis: We hypothesize *Gas5* is a cell-type specific modulator in brain of ethanol-related molecular and behavioral phenotypes, specifically through its regulation of GR.

Methods: *In vitro,* we are performing RNA Sequencing on primary microglia, astrocyte, and neuron cultures from neonatal C57BL/6J male and female mice +/- *Gas5* KD and +/- 24-hour ethanol exposure. *In vivo,* we infused an AAV2 containing a *Gas5* overexpression cassette in NAc of male and female mice, then assessed voluntary ethanol consumption via 2BC.

Results: *In vitro* immunocytochemistry and fluorescence activated cell sorting (FACS) results confirmed >90% purity of microglia and astrocyte cultures. RT-qPCR verified successful (80%) *Gas5* knockdown in microglia. All cultures will undergo RNA sequencing to assess *Gas5* modulation of ethanol-induced GR-responsive gene transcription. *In vitro* purity, RT-qPCR results, and available RNA-sequencing data will be presented. *In vivo, Gas5* overexpression in NAc did not alter voluntary ethanol consumption nor preference in non-ethanol dependent male or female mice.

Conclusions: Available data suggest sex-, cell type-, brain region-, and ethanol dependence-specific functioning of *Gas5* in brain in ethanol-related phenotypes that will be elucidated with further *in vitro* and *in vivo* studies.

Significance: AUD research almost exclusively focuses on protein-coding genes, and existing AUD medications target behavioral outcomes, not AUD pathogenesis. By examining the functioning of a noncoding RNA in ethanol-related phenotypes, this work may lead to more effective AUD treatments.

Research/Grant Support: We gratefully acknowledge NIAAA grants AA020889 (MPI: Sean Farris & Gregg Homanics), AA030257 (PI: Sean Farris), and AA031168 (PI: Rachel Rice).

Abstract 22

COGNITIVE PERFORMANCE AND PAIN PERCEPTION WITH PROPOFOL, DEXMEDETOMIDINE, AND FENTANYL IN HEALTHY YOUNG ADULTS

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Introduction: This comparative analysis aims to investigate the differential effects of propofol, dexmedetomidine, and fentanyl on attention, memory, and pain perception in healthy young adults.

Hypothesis: We hypothesize that memory performance will be significantly reduced by propofol, and that reported pain will be significantly reduced by fentanyl.

Methods: This was a randomized single-blind crossover study of adults < 40 yrs, comparing low doses of propofol (n=19), dexmedetomidine (n=25), and fentanyl (n=25) to saline. A steady-state effect-site concentration was targeted. Nerve stimulation was delivered periodically, at a level set in advance to 7/10 intensity. Pain scores were recorded from subjects during a combined memory and pain task, in which, words were paired with electrical shocks at random. Pain scores were additionally recorded from a block-design fMRI task scan with five 10 s painful acute stimulations. A memory encoding experiment involved exposure to several experimental cues (typically recorded tones and spoken words). Some of the cues were paired with a painful shock, and the order of these randomized among other non-pain-paired cues. An image recognition task, free from shocks, was performed by showing a series of complex geometric colored shapes presented every 5 s. Attention was assessed with a 3-back task, and memory was assessed by identifying new or old shapes presented > 60 s later. Long-term memory testing was the next day. Performance was determined using the signal detection metric d´ compared across drug condition. Linear mixed modeling was used to account for within-subject framework and some missing data pairs.

Results: Attention was reduced under dexmedetomidine, with a 38% decrease in performance on the 3-back task. Recognition memory performance was reduced 42% under propofol and 29% under dexmedetomidine. Both fentanyl and propofol reduced ratings of pain intensity by 8%. Pain unpleasantness ratings were reduced 16% under propofol and 13% under fentanyl.

Conclusions: Even at low doses, performance on tasks spanning different cognitive domains varied considerably between these diverse drugs. This reveals non-uniformity in the impact distinct agents have on different aspects of conscious experience, and similar methodology can be used I future work to help better understand how these work in combination.

Significance: In addition to added to our basic knowledge of cognitive effects of specific anesthetics, these findings could help guide anesthetic selection in settings where cognitive performance is intended to be retained, while alleviating pain (e.g. awake craniotomy).

Research/ Grant Support: R35GM146822 (PI: Keith Vogt, MD, PhD)

Abstract 23

METHYLENE BLUE ADMINISTRATION IN LIVING DONOR LIVER TRANSPLANT RECIPIENTS IS ASSOCIATED WITH REDUCED INCIDENCE OF POSTOPERATIVE ACUTE KIDNEY INJURY

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Introduction: Acute kidney injury is a common complication after liver transplantation. Methylene blue (MB) has been shown to attenuate hemodynamic changes with reperfusion during liver transplant (LT) and is protective against AKI in cardiac surgery. However, the efficacy of MB in preventing AKI in LT remains unclear. This study investigates whether pre-reperfusion administration of MB decreases the incidence of postoperative AKI in LT patients.

Hypothesis: We hypothesize that pre-reperfusion administration of MB decreases the incidence of postoperative AKI by mitigating hypotension during reperfusion during LT.

Methods: This is a single-center, retrospective cohort study of 415 patients who underwent living-donor LT between January 2018 to June 2023. The MB group included patients who received a bolus of 1-1.5 mg/kg of MB just prior to graft reperfusion, while the control group did not. The primary outcome was incidence of postoperative AKI as staged via the KDIGO guidelines. Secondary outcomes included postreperfusion hemodynamic parameters, incidence of post-reperfusion syndrome (PRS), intraoperative vasopressor use, incidence of early allograft dysfunction (EAD), hospital length of stay (LOS), and mortality. Logistic regression was used to identify independent predictors of AKI (both stage I and all stages). Repeated measures ANOVA was used to analyze postreperfusion hemodynamics.

Results: Of the 415 patients, 317 were included in the MB group and 98 patients were included in the control group. The preoperative characteristics of each group were not significantly different. The incidence of postoperative AKI stage I and AKI all stage was significantly lower in the MB relative to control (AKI stage 1; 74 (23.3%) vs. 170 (34.7%), p=0.03, AKI all stage; 95 (30.0%) vs. 40 (40.8%), p=0.045). Multivariate regression showed that MB was independently associated with AKI stage I (OR: 0.59, 95% CI 0.36-0.99, p=0.046). In terms of secondary outcomes, the incidence of EAD was significantly lower in the MB group compared to the control group (53 (16.9%) vs. 27(27.6%), p=0.02). Hospital LOS, mortality, incidence of PRS, postreperfusion hemodynamics and vasopressor use were not significantly different between the groups.

Conclusions: We found that MB administration prior to reperfusion in living-donor LT is independently associated with reduced incidence of postoperative AKI stage I. Furthermore, MB administration was associated with decreased incidence of EAD.

Significance: To our knowledge, this is the only study to demonstrate an association between MB administration and reduced incidence of postoperative AKI stage I. AKI stage I is common after liver transplant, and we have identified MB administration as a modifiable risk factor to aid in prevention of AKI in this population.

Research/Grant Support: This study was approved by the University of Pittsburgh Institutional Review Board (STUDY20050148).

Abstract 24

COMPARISON OF MRI, RETINAL, AND COGNITIVE OUTCOMES IN WOMEN WITH AND WITHOUT HYPERTENSIVE DISORDERS OF PREGNANCY

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Introduction: There is growing evidence that women with hypertensive disorders of pregnancy (HDP) are at risk of long term cognitive decline including dementia, possibly due to changes in brain structure and microvasculature. The UK BioBank prospectively recruited 500,000 people in the United Kingdom between the ages of 40-69 from 2006-2010, and collected medical, lifestyle, imaging and genetic data, offering a unique opportunity to investigate whether there are cerebrovascular changes in women with HDP.

Hypothesis: Compared to non-HDP controls, women with history of HDP will have changes in: structural MRI, retinal measurements, and cognition.

Methods: We used UK Biobank data from women who had at least 1 live birth and MRI data, excluding any brain or neurological pathology (such as stroke, epilepsy, Alzheimer's disease); this included 9911 women, 94 with HDP. Our outcome of interest included summarized brain MRI measurements, retinal measurements by Optical Coherence Tomography, and objective cognitive testing. We created a 15:1 age-matched dataset for analysis. Continuous variables were analyzed using two-sample t-tests, and categorical variables were analyzed using chi-square tests or Fisher's Exact Test. Univariate linear regression was used to investigate the association between outcome variables and age. Multiple comparisons were adjusted for using Benjamini-Hochberg correction. All analyses were performed in R 4.4.3.

Results: Mean age at recruitment was 53.7 years in non-HDP patients, compared to 44.1 years in HDP patients. In the unmatched dataset, mean cerebral blood flow in frontal lobe grey matter (right $p=0.023$, left $p=0.0084$), total volume of white matter hyperintensities ($p=0.0043$), and peri-ventricular white matter hyperintensities ($p=0.001$), volume of ventricular cerebrospinal fluid ($p<0.0001$), volume of grey matter ($p<0.0001$), reaction time ($p=0.0008$), and symbol digit matching ($p=0.0016$) were worse in the non-HDP group. There were no significant differences in mean retinal measures. In our univariate models, age was significantly associated with worsening of most MRI and cognitive measures. In the age-matched dataset, none of the MRI, retinal, or cognitive variables were significantly different ($P>0.05$).

Conclusions: The differences seen initially between HDP and non-HDP women are likely due to the confounding effect of age. Thus, using UK Biobank data, we are unable to demonstrate that hypertensive disorders of pregnancy are associated with changes in brain structure, retinal measurements, or cognitive function, after accounting for patient age. Limitations include: 1) exposure was based on ICD codes from inpatient records, 2) UK-only sample may not generalize to the rest of the world 3) non-HDP group may have additional co-morbidities affecting the cerebral vasculature, 4) time of brain imaging was remote from pregnancy, and 5) further analysis is needed regarding how cerebrovascular sequelae such as stroke affect these outcomes.

Significance: While we were unable to find evidence supporting our hypothesis in the UK Biobank, more prospective and longitudinal studies need to recruit during pregnancy at the acute phase of the disease to accurately assess the effect of HDP on the brain.

Research/Grant Support: SOAP-FAER MRTG

Abstract 25

MICROELECTRODE ARRAYS WITH INTEGRATED ENZYME-BASED BIOSENSORS FOR NEUROTRANSMITTER DETECTION IN THE DORSAL ROOT GANGLION

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Introduction: Chronic pain is a condition that affects nearly twenty percent of the world population and is described as pain that regularly restricts routine life and/or work activities and generally decreases an individual's quality of life. Chronic pain is also associated with an increased risk of opioid misuse, depression, and anxiety. In contrast to acute pain, which plays a protective and adaptive role and typically resolves after healing, chronic pain endures beyond the normal healing process and is maladaptive as it serves no known biological purpose. Ascending somatosensory input from the skin and visceral organs is detected by sensory neurons whose soma resides in the dorsal root ganglion (DRG). As the DRG is a locus of somatosensory input from the peripheral nervous system, it is of particular interest in the development of chronic pain at a mechanistic level. While there are no traditional synapses between neurons in the DRG, SGCs express glutamate and gamma-aminobutyric acid (GABA) transporters and have been shown to receive and secrete these neurotransmitters within the local extracellular space as a method of neuromodulation. Upon injury or inflammation, SGCs can enter an activated phenotype that alters healthy SGC function and directly contributes to neuronal sensitization and the development of chronic pain. However, the dynamics of glutamate and GABA within the DRG remain to be fully understood in the context of chronic pain. Additionally, there are very few studies that provide neurotransmitter detection within intact DRGs.

Hypothesis: Thus, we hypothesize that there are measurable neurotransmitters released in the DRG and that the concentrations of these neurotransmitters may be different between naïve and chronic pain model animals.

Methods: Here, we present a flexible microelectrode array (MEA) integrated with enzyme-based biosensors to enable real-time amperometric detection of neurotransmitters glutamate, GABA, and glycine within biological tissues.

Results: By utilizing our enzyme biosensors, we have successfully observed neurotransmitter release in intact electrically stimulated DRGs from naïve and spared-nerve animals which may indicate differences in neurotransmitter release and concentration in chronic pain models.

Conclusions: We believe that these differences in neurotransmitter release may indicate one way that the interplay between activated SGCs and sensitized neurons in the DRG contribute to the development of chronic pain.

Significance: This technology and the results of this study may enable more targeted and precise monitoring and treatment of chronic pain at the neurotransmitter level and expand our understanding of the mechanisms of the DRG in the development of chronic pain.

Research/Grant Support: NIH R01NS136622 (PI: Tracy Cui), NIH T32GM075770 (PI: Yan Xu)

DEPARTMENT OF CRITICAL CARE MEDICINE

Abstract 26

IRG1 KNOCKOUT INCREASES EXPRESSION OF NLRP3 INFLAMMASOME-RELATED GENES IN MICROGLIA AFTER CONTROLLED CORTICAL IMPACT

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Introduction: Itaconate is an immunometabolite of the Krebs cycle found in myeloid cells and is a direct endogenous inhibitor of the NLRP3 inflammasome. Our objective was to evaluate expression of NLRP3 inflammasome-related genes in microglial from pericontusional tissue of IRG1$^{-/-}$ mice after controlled cortical impact (CCI).

Hypothesis: We hypothesized that knockout of Immunoresponsive Gene 1 (IRG1), which is required for production of itaconate through cis-aconitate decarboxylation, would increase NLRP3 inflammasome activation.

Methods: CCI was performed in adult male (C57BL/6NJ-Irg1) global knock-out and wild-type (WT) mice (5m/s, 1.2 mm depth). Mice (n=3/group) were sacrificed on post-injury day 7 and microglia isolated from pericontusional tissue. RT-PCR was performed on microglial RNA for NLRP3-related gene expression analysis. Student's t-test was performed ($p<0.05$).

Results: CCI increased expression of nlrp3, casp1, il1b, and il18 compared to naïve in both WT and IRG1$^{-/-}$ mouse microglia 7 days post-injury. Expression of il1b was 3.7-fold greater ($p<0.05$) and il18 was 3.8-fold greater in IRG1$^{-/-}$ mice microglia vs WT after CCI. There was increased IL-18 expression in CCI WT vs KO (<0.0001), Caspase-1 (0.050), and IL-1B (0.04). There was a trend towards increased expression of nlrp3 ($p=0.09$) and casp1 ($p=0.05$) after CCI in IRG1$^{-/-}$ mouse microglia vs WT. No differences were observed between WT vs IRG1$^{-/-}$ naïve.

Conclusions: Global knockout of IRG1 increased expression of NLRP3 inflammasome-related genes in microglia 7 days after CCI. Given the important role of microglia in secondary injury and repair after TBI, our exploratory study suggests that further investigation of the role of IRG1 and itaconate is warranted.

Significance: There may be a more nuanced role of itaconate and IRG1 relating to neuroinflammation after CCI. Future investigations into IRG1 knockout and microglial polarization may prove beneficial.

Research/Grant Support: 5T32HD040686 R01 NS127372

Abstract 27

RACE AND TREATMENT AND OUTCOMES IN CHILDREN WITH LIFE-THREATENING HEMORRHAGE

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Introduction: Race and ethnic disparities are associated with many leading causes of pediatric mortality. Data are sparse regarding racial differences in treatment and outcomes in children with life-threatening hemorrhage.

Hypothesis: Mortality rates from life-threatening hemorrhage may be higher in traditionally marginalized races and ethnicities.

Methods: This is a secondary analysis of a multicenter prospective observational study of massive transfusion in children (MATIC). The primary outcome is the relationship between self-reported race and 28-day mortality. Secondary endpoints are 6 hr and 24 hr mortality. Chi-square testing, univariate, weighted Cox proportional hazards regressions, and Kaplan-Meier survival plots were used for adjusted analyses.

Results: Of 449 children, the median age was 7.3 years, 55% were male, and the median ISS was 29. In this cohort, 221 (49%) identified as non-Hispanic white, 107 (24%) as non-Hispanic Black, 43 (10%) as Hispanic, 19 (4%) as “other” race, and 59 (13%) as unknown race. Higher PRISM score, fixed and dilated pupils, age < 1 year, and medical bleeding were associated with higher risk of 28-day mortality (adjusted $p < 0.05$ for each). Risk factors were similar across race groups, except for bleeding etiology, which was more frequently traumatic in non-Hispanic Black patients. Patients with “unknown” race had >2-fold greater adjusted hazard ratios (HR) for mortality at 6 hr, 24 hr, and 28 days when compared to non-Hispanic whites (HR 2.4, 95% CI [1.1, 5.1]; 2.7 [1.5, 5.0]; and 2.1 [1.2, 3.7], respectively). There was a higher 28-day mortality in Hispanic patients versus non-Hispanic whites in the adjusted multivariate model (HR 1.7, 95% CI [1.0, 2.9]). Patients in the unknown race and Hispanic subgroups were least often treated with antifibrinolytics and factor concentrates (8.5% and 18.6%, respectively). After adjustment, there were no differences in the transfusion ratios of plasma:pRBC and platelet:pRBC by race.

Conclusion: Patient race may have a subtle association with long-term survivability and management of life-threatening hemorrhage.

Significance: Future studies are needed to define optimal management to promote equitable care and improved outcomes in the treatment of children with life-threatening hemorrhage.

Research/Grant Support: None.

Abstract 28

PERFORMANCE OF DAY 1 PEDIATRIC LOGISTIC ORGAN DYSFUNCTION-2 SCORE IN A PEDIATRIC TRAUMA POPULATION

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Introduction: Scoring systems for multiorgan dysfunction, such as The Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score, show good discrimination and calibration in a general pediatric intensive care unit (PICU) population for predicting mortality. The performance of the admission (day 1) PELOD-2 score in predicting mortality for the subpopulation of critically ill pediatric trauma patients is unknown.

Hypothesis: We predict that the PELOD-2 score will have acceptable performance in our patient population.

Methods: This single center retrospective study included all pediatric trauma patients admitted to a tertiary care center PICU from January 2021-March 2024. PELOD-2 scores were calculated via the electronic medical record on admission. The primary outcome was mortality during hospital admission. Performance of the PELOD-2 score was analyzed by discrimination via the area under the receiver operating characteristic curve (AUROC) and area under the precision recall curve (AUPRC). The precision recall curve has been utilized in the context of imbalanced data and is determined by the positive predictive value (precision) on the Y axis and the sensitivity (recall) on the X axis. Calibration was determined via the Hosmer–Lemeshow test.

Results: Of 589 pediatric trauma patients, the median age was 3.17 (interquartile range [IQR] 0.33 – 11.7) years and hospital mortality was 5.7% (34/589). Day 1 PELOD-2 scores were higher in non-survivors as compared to survivors (21.0 [18.0-23.8] vs 2.0 [2.0 – 7.0], $p < 0.001$). Day 1 PELOD-2 score had an AUROC of 0.91 (95% confidence interval, 0.85 – 0.98) and AUPRC of 0.61 (0.47-0.84). Calibration resulted in a Chi-square of 4.17 and p= 0.24.

Conclusions: Overall, day 1 PELOD-2 score has good discrimination and acceptable calibration, indicating that this initial score is highly predictive of mortality in the critically ill pediatric trauma population. These results suggest the PELOD-2 score on day 1 may be considered as a surrogate for severity of injury in this population. Validation of these results are required in large multicenter populations as well as further evaluation of the performance of the PELOD-2 score in predicting mortality throughout subsequent ICU admission days.

Significance: The performance of the PELOD-2 score in pediatric trauma patients further supports the use of this score as an outcomes measure in ongoing clinical trials.

Abstract 29

PERFORMANCE OF THE PEDIATRIC RISK OF ILLNESS MORTALITY EVALUATION (PRIME) AT A QUATERNARY CHILDREN'S HOSPITAL

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Introduction: There is an ongoing need for generalizable population-level risk adjustment models within intensive care and an urgent need to update pediatric models, which were developed based on data from over 10 years ago. Real world data sources, such as the electronic health record (EHR), offer the ability to readily incorporate more information into risk adjustment models.

Hypothesis: Curated electronic health record data can be used to develop high performing standardized mortality ratios for children admitted to the pediatric intensive care unit (PICU)

Methods: This is a retrospective cohort study of diagnostically diverse admissions a quaternary PICU from October 2015-December 2021. EHR data were curated from the first 24 hours of PICU admission. Patients were assigned randomly to training or test datasets, representing 70% and 30% of data, respectively. Using training data, a ridge logistic regression model was built and model turning was performed using 10-fold cross- validation. This model was then used to calculate a probability of mortality for each patient encounter in the test dataset. Model performance was assessed by examining area under the receiver operating curve (AUROC), the area under the precision recall curve (AURPC), standardized mortality ratios (SMR), calibration plots, Brier scores, and the Hosmer-Lemeshow test. Data are presented with counts (%), medians (interquartile range), and 95% confidence intervals.

Results: There were 15241 encounters with 286 (1.9%) deaths. 6738 (44.2%) of patients were female and median age was 6 (1-13), with no significant differences between the training and test dataset. There were 7964 (52.2%) admissions from the emergency department , 2786 (18.2%) from other hospitals, 2260 (14.8%) from acute care, 1918 (12.5%) post-operatively, and 313 (2.1%) from other intensive care units. The most common reasons for admission were respiratory (5365, 35.2%) and injury and toxic ingestion (2093, 13.8%). The PRIME demonstrated excellent discrimination with an AUROC of 0.93 [0.91-0.96] and an AUPRC of 0.46 [0.35-0.57]. Visualized calibration was good, the Hosmer-Lemeshow goodness of fit statistic had a non-significant p-value of 0.47, the SMR was 1.0, and Brier score was 0.013.

Conclusions: In a diagnostically diverse cohort of critically ill children, the PRIME demonstrated excellent performance and calibration.

Significance: This provides additional evidence that interoperable EHR data can be leveraged to efficiently facilitate risk adjustment. Future steps include development and validation a suite of severity of illness scores in an international cohort, with benchmarking against existing scores, and use of PRIME to evaluate differences in outcomes among different patient populations and for quality improvement initiatives

Research/Grant Support: None

Abstract 30

LINOLEIC ACID IN ENTERAL FEEDING AND ACUTE KIDNEY INJURY IN CRITICALLY ILL PATIENTS

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Objectives: Linoleic acid (LA), the most important dietary omega-6 polyunsaturated fatty acid, has been associated with inflammation and chronic illnesses, but studies in acute settings are lacking. The goal of this study was to investigate the effect of LA administration, as a component of enteral feeds, on development of acute kidney injury (AKI) in a critically ill adult population.

Methods: We performed a retrospective cohort study in adult critically ill patients, admitted to any of the 16 hospitals within the University of Pittsburgh Medical Center network in Pennsylvania, between January 2010 to June 2018. Only the first encounter was considered if a patient had multiple visits. Enteral feeding formulas were obtained, and total amounts were calculated for individual products daily for the first 7 days of hospital stay. LA content was obtained for each product based on manufacturer's publicly available nutrition information data. AKI was defined in accord with the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Persistent severe AKI was defined as KDIGO stage 3 lasting for at least 72h. Analyses were adjusted for demographic characteristics, total energy administered in enteral nutrition, comorbidities and severity of illness scores.

Results: A total of 23,536 patient encounters were eligible and included in the final analysis. Mean age was 63.5 (SD 16.2), 10,531 (44.7%) were female, and 6,864 (29.2%) had diabetes. Sepsis was present on 13,071 (55.5%), with 9,724 (41.3%) of patients having vasopressor-dependent shock. Mean energy in Kcal administered in the first 7 days was 3,230 (SD 4,120). LA administered mean was 22.3g (SD 27.6) in 7 days. LA was independently associated with AKI (OR 1.61, 95%cI 1.37-1.91, p <0.001), renal replacement therapy (OR 1.49, 95%CI 1.26-1.76, p <0.001), persistent severe AKI (OR 2.62, 95%CI 2.16-3.16, p <0.001), and intensive care unit length of stay (OR 1.10, 95%CI 1.06-1.15, p <0.001). LA was not significantly associated with 28-day mortality or in-hospital mortality. Sensitivity analyses did not substantially modify above results.

Conclusions: LA was associated with the development of persistent severe AKI, need for renal replacement therapy, and intensive care unit length of stay. These results agree with prior findings from our group associating LA plasma levels with AKI in sepsis in a different cohort.

Abstract 31

ICP RESPONSIVITY, A NOVEL METRIC FOR SIMULTANEOUS ASSESSMENT OF CEREBROVASCULAR AUTOREGULATION AND INTRACRANIAL COMPLIANCE IN PEDIATRIC PATIENTS WITH SEVERE TBI

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Introduction: Intracranial pressure (ICP) typically remains stable during minor physiological fluctuations in cardiovascular dynamics and CO2 levels. However, under pathological conditions such as severe traumatic brain injury (sTBI), systemic physiological changes can cause alterations in ICP, indicating disturbed autoregulation and/or poor intracranial compliance. We introduce a quantitative metric, ICP responsivity (RICP), derived from high-frequency physiological signals, and describe its characteristics in pediatric sTBI patients.

Methods: This IRB-approved study analyzed 0.2 Hz bedside monitor data from 21 prospectively enrolled children (4 mo - 15 y, 62% male) with sTBI (initial GCS < 8, median GCS: 4 [IQR 2.5]) at a large children's hospital. Penalized regression models were developed using ICP data with heart rate, mean arterial pressure (MAP), and end-tidal CO2 (ETCO2) as predictor variables. A 6-hour weighted rolling window with normalized variables was used to derive a time-varying RICP (calculated as the R^2 value of the model fit) and regression coefficients for MAP, HR, and ETCO2.

Results: ICP was generally more responsive to changes in underlying physiological signals in patients that died vs survived (RICP: 0.58 vs. 0.39, p=0.08). Further, changes in ICP tended to be positively driven by changes in MAP in patients that died vs survived (MAP coefficient: 0.32 vs. 0.05, p=0.13). CO2 reactivity was higher in patients that survived vs died (CO2 coefficient: 0.36 vs. 0.08, p=0.04). Across all patients, when CPP was below the lower limit of autoregulation, ICP was more responsive and driven by changes in MAP (RICP: 0.67 [0.46-0.84] vs 0.38 [0.19-0.60], MAP coefficients: 0.64 [0.25-0.82] vs 0.06 [-0.15-0.30] for CPP<50 vs CPP>50). Similarly, CO2 reactivity was higher with CPP>50 mmHg vs CPP<50 mmHg (ETCO2 coefficients :0.31 [0.03-0.60] vs. 0.08 [-0.10-0.32]).

Conclusions: Mortality in patients with severe TBI correlates with ICP responsivity to changes in MAP, suggesting prolonged periods of pressure passive BP autoregulation experienced by these patients. Pressure passive ICP response to changes in MAP is further confirmed in the data where CPP is below the limit of autoregulation. In patients that survived, or when CPP is above the autoregulatory limit, ICP is less responsive to changes in MAP and instead correlates with changes in ETCO2 suggesting intact CO2 reactivity.

Significance: Overall, these findings suggest that the RICP model can capture real-time dynamic intracranial physiology in TBI patients, prompting its further development for providing clinical decision support at the bedside.

Abstract 32

DEVELOPMENT OF AN EHR-EMBEDDED DIGITAL SAFETY NET TO REDUCE CRITICAL DETERIORATION EVENTS AMONG ACUTE CARE PATIENTS

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Introduction: Children on acute care floors are at risk for critical deterioration, including in-hospital cardiac arrest, extracorporeal therapies, urgent ICU transfer, and death. Vasoactive use and non-invasive or invasive ventilation in these patients are linked to a 13-fold increase in mortality.[1] Such events add an estimated $100,000 per admission,[2] prolong ICU stays, and raise in-hospital mortality.[3] At our quaternary children's hospital, mortality rose to 2.5 per 10,000 patients in 2018, prompting efforts to identify at-risk patients earlier using existing tools.

Hypothesis: Deployment of an EHR-embedded deterioration prediction model would reduce critical deterioration events in pediatric acute care patients.

Methods: Between 2017 and 2018, a two-level sepsis screening protocol was implemented across acute care units. This protocol combined a rule-based electronic health record (EHR) trigger tool with a subsequent bedside huddle and sepsis order set. Building on its success, a broader clinical deterioration prediction score was developed, incorporating both clinical data and the intuitive assessments of experienced nurses. Using all 2017 patient admissions, a random forest model was created to predict a composite outcome representing life-threatening clinical deterioration. The model was then integrated into the EHR. Since its initial deployment, iterative Plan-Do-Study-Act (PDSA) cycles have been employed to refine both the model's predictive performance and its integration into clinical workflows.

Results: Following model optimization, the random forest model demonstrated strong performance, with a c-statistic of 0.80, an area under the precision-recall curve (AUPRC) of 0.20, and a number needed to alert (NNA) of 4. Deployment of the sepsis and shock screening workflow was associated with a significant reduction in critical deterioration events, with rates declining from 2.5 per 10,000 admissions in 2018 to 0.2 per 10,000 admissions between 2019 and 2022 ($P < 0.001$). Moreover, during the deployment period, there was a 31% net reduction in mortality among patients transferred to the ICU.

Conclusions: The development of a sequential clinical deterioration prediction model—leveraging machine learning techniques, legacy patient data, and provider intuition—was associated with improved critical deterioration outcomes at our quaternary children's hospital. Not only did the rate of deterioration events decline, but outcomes also improved among patients who still experienced critical deterioration despite preventive efforts. Continued refinement and optimization of the model may further support clinicians in the early recognition and timely resuscitation of pediatric shock.

Significance: Implementation of an EHR-embedded deterioration prediction tool was associated with a significant reduction in critical deterioration events among acute care pediatric patients.

Research/Grant Support: NIH 5T32HD040686-23 (PI: Kochanek and Clark)

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Abstract 33

AN EARLY MULTIMODAL MODEL FOR 1 YEAR OUTCOME AFTER PEDIATRIC CARDIAC ARREST

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Introduction: Therapeutic interventions and family counseling after pediatric cardiac arrest (CA) depend on the ability to provide early and accurate outcome prognostication. We aimed to determine if the addition of blood and imaging biomarkers of brain injury to clinical predictive models increased outcome prediction accuracy after pediatric CA.

Hypothesis: We hypothesize that blood and imaging biomarkers will improve clinical model predictive accuracy for 1 year outcome after pediatric CA.

Methods: This is a secondary analysis of the Personalizing Outcomes after Child Cardiac Arrest (POCCA) study that evaluated children <18 years with intensive care unit admission after a CA. Demographic variables (age, sex, race), CA characteristics (CA etiology, location of CA, witnessed status), and illness severity (Pediatric Index of Mortality 3 score) were selected as clinical predictors. Glial fibrillary acidic protein, ubiquitin carboxyl-terminal esterase L1, neurofilament light and tau were measured in blood samples at 24 hours post-CA. Magnetic Resonance Imaging (MRI) Injury Score was utilized as a summated score of brain imaging obtained within 2 weeks post-CA. The primary outcome was unfavorable outcome (death or Vineland Adaptive Behavior Scale <70) at 1 year post-CA. Missing outcomes and covariate values were imputed via multiple imputation by chained equations. Likelihood ratio tests were performed to compare the predictive ability of the model including clinical predictors with or without biomarker data. Four alternative models developed using a validation cohort that excluded patients with unobserved outcome or biomarker data were compared for their predictive accuracy of primary outcome. A bootstrap procedure was used to obtain optimism-corrected estimates and 95% confidence intervals of the area under the receiver operating curve (AUROC), calibration intercept and calibration slope for each modeling procedure. The prediction cohort was used to assess if the addition of MRI Injury Score to the model including both clinical predictors and biomarker data significantly improved model fit.

Results: 163 children were enrolled in the POCCA study. 43 children were missing outcomes, 2 were missing biomarker data, 13 were missing CA etiology, and 30 were missing MRI Injury Scores that were imputed. 118 children with 24h biomarker data and clinical variables available were included into a prediction cohort for comparison. When added to the model with clinical variables, blood biomarker variables significantly improved model fit compared to clinical variables alone (p=0.001). In the prediction cohort, a penalized regression model demonstrated superior predictive performance of 1 year outcomes, with an optimism-corrected AUROC of 0.863 (95% CI, 0.83-0.95), calibration intercept of 0.046 (95% CI, 0.00-0.31), and calibration slope of 1.074 (95% CI, 1.02-1.54). Further addition of MRI Injury Score to the model including clinical predictors and blood biomarkers tended towards improvement (p=0.07).

Conclusions: The addition of blood-based brain injury biomarkers to readily available CA predictors significantly improved the predictive accuracy of a clinically feasible multimodal model for 1 year outcome after pediatric CA. Further modification and external validation of this multimodal model is essential for future implementation.

Significance: This study represents an improvement of a predictive multimodal model for children after CA that includes both clinical variables and blood-based brain injury biomarkers with a goal to provide early, accurate outcome prognostication to families and caregivers.

Research/Grant support: R01NS096714 (PI: Ericka L Fink, MD)

DEPARTMENT OF EMERGENCY MEDICINE

Abstract 34

CHARACTERISTICS OF EMERGENCY DEPARTMENT PATIENTS WITH PAIN: A NOVEL REMOTE RESEARCH STUDY IN 10 PENNSYLVANIA EMERGENCY DEPARTMENTS

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Introduction: Despite longstanding recognition of individual disparities in acute pain presentation and management, individuals affected by these inequities are frequently underrepresented in research. We are enrolling a large cohort of patients from emergency departments (ED) in Pennsylvania (PA) to characterize social determinants of health (SDOH). The aims of this study were twofold: 1) to determine the feasibility of remote recruitment of ED patients in pain; and 2) to describe participants in terms of SDOH.

Hypothesis: We hypothesize that among ED patients in pain, a significant number will report socioeconomic disadvantages and barriers to accessing timely healthcare.

Methods: ED patients with a pain score of at least 4/10 were eligible and invited to complete an online survey in the ED or within 48-hours (enrollment is ongoing); to date, 401 patients (M age = 36.5; range: 18-88) from 11 participating hospitals across Pennsylvania voluntarily enrolled for the study and completed the baseline survey. Sociodemographic data (gender, race, education, employment, and income), reasons for seeking ED treatment, pain characteristics, and barriers to healthcare access were among the variables collected.

Results: Among 2790 patients that completed the study screening, 1776 were eligible and 1172 consented and enrolled into the study (66% of those eligible); 791 completed the baseline survey assessment (68% of those who consented). The cohort is predominantly female (71%), White (72%) or Black (28%), with at least high school (31%) or some college education (>62%); 25% report unemployment. Approximately 33% report income falling below the 2024 federal poverty line. Reasons for seeking ED treatment ranged from ongoing (41%) to new health problems (37%), or acute accident or injury (22%). On average, pain score was 7.14 (SD = 1.80) out of 10. In the past year, ED participants reported various barriers to accessing healthcare: couldn't get a timely appointment (28%), worry insurance won't cover cost (24%), worry about cost of medication (22%), work/family responsibilities (21%) and transportation problems (20%). These barriers were associated with SDOH; in general, pain scores were higher for nonwhite participants and those with income below the poverty line.

Conclusions: Our findings support the feasibility of remotely enrolling ED patients into a pain-related study, highlight the barriers to accessing healthcare among this population, and suggest that SDOH are associated with differences in pain severity and barriers to care. These results may serve to identify opportunities to optimize and reduce disparities in pain-related and health outcomes of ED patients.

Significance: These results may inform future approaches for equitable access and management of pain care in emergency medicine settings.

Research/Grant Support: Pennsylvania Department of Health Commonwealth Universal Research Enhancement Program (CURE).

Abstract 35

CRITICAL CARE NURSES' DECISION-MAKING TO ENGAGE PATIENTS WITH ACUTE BRAIN INJURIES IN EARLY MOBILITY: A MINI-GROUNDED THEORY STUDY

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Introduction: Nurses engaging patients with acute brain injuries in early mobility has many positive effects, including reducing known complications of critical illness. The literature encompasses quality improvement and studies of multidisciplinary teams identifying perceived barriers to early mobility. This has shown that patients eligible for early mobility are not always given this care. Patients critically ill with acute brain injuries are already at high risk of dying and are rendered especially vulnerable as they are often unable to communicate their needs. This study aims to explore critical care nurses' decision-making processes concerning early mobility for patients with acute brain injuries in the intensive care unit (ICU).

Research question: What process do critical care nurses follow when deciding to engage patients with acute brain injuries in early mobility?

Methods: This mini-study utilized the Corbin and Strauss approach to grounded theory. All interviews were conducted and recorded via Zoom using a semi-structured interview guide. The data were analyzed using an iterative and constant comparative method related to the inductive reasoning of grounded theory. Data were collected and coded in MAXQDA.

Results: There were three study participants, so only axial coding was performed. All three participants were female and had seven to ten years of nursing experience. Nineteen open codes emerged, leading to three axial codes representing factors in nurses' decision-making processes. These codes addressed concerns regarding patient and staff safety, the ethos and professional practice style of nurses, as well as the effects of the patient's illness and their response to mobilization.

Conclusions: This mini-study revealed initial findings on critical care nurses' decision-making processes regarding early mobility following acute brain injury. However, additional open codes gathered from further participant interviews and analyses will yield more axial and selective codes for developing a new theory. These preliminary results indicate that the nurses' decision-making process is multifaceted; further data will elaborate on this. While this study suggests that a larger-scale research project is feasible, a comprehensive grounded theory study is essential for a deeper understanding of this process.

Significance: When nurses involve patients with acute brain injuries in early mobility, it may decrease the incidence of infections and pressure ulcers, enhance motor recovery, and, at best, boost survival rates. The exploration and understanding of critical care nurses' decision-making processes regarding the engagement of patients with acute brain injuries in early mobility will inform the development of a theoretical decision-making model. This will facilitate a wider implementation of this evidence-based intervention.

Research/Grant Support: N/A

Abstract 36

TEMPORALIS MUSCLE THICKNESS CORRELATES WITH PREMORBID CLINICAL FRAILTY IN PATIENTS WITH SEVERE ACUTE BRAIN INJURY

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Introduction: Previous studies have associated frailty with mortality in critically ill patients. The Clinical Frailty Scale (CFS) is the most used global measure of premorbid frailty in critically ill patients; however, there is no established gold standard. Temporalis muscle thickness (TMT) is a measure of sarcopenia that can be measured on head computed tomography (CT) and may represent a specific component of physical frailty.

Hypothesis: TMT is inversely correlated with premorbid frailty in patients with severe acute brain injury (SABI).

Methods: We enrolled adult patients who were admitted to the intensive care unit after SABI and had a head CT obtained within 48 hours of injury. We defined SABI as ischemic stroke, intraparenchymal hemorrhage/intraventricular hemorrhage (IPH/IVH), subarachnoid hemorrhage (SAH), or traumatic brain injury (TBI) resulting in a highest Glasgow Coma Scale ≤ 12 within the first 24 hours of injury. Study investigators prospectively obtained premorbid CFS through patient or surrogate interview using a standard instrument. A blinded study investigator then reviewed head CTs and measured TMT bilaterally at a level 5mm above the superior orbital rim, adjacent to the Sylvian fissure. We then averaged the two measurements within each patient. We summarized patient demographics with descriptive statistics. We calculated Spearman rank correlation to assess the relationship between average TMT and CFS.

Results: Of the 33 subjects included, the median age was 65 (IQR 49-73), with 17 (52%) being female. 7 (21%) participants suffered ischemic stroke, 13 (39%) suffered IPH/IVH, 9 (27%) suffered SAH, and 4 (12%) suffered TBI. The mean TMT in this cohort was 6.3 mm (SD 1.6), and the median CFS was 3 (IQR 2-4). We found a weak negative correlation between TMT and CFS, $r = -0.31$, $p = 0.08$.

Conclusions: Our findings suggest that lower TMT is associated with higher CFS, providing criterion validity that objective sarcopenia contributes to global frailty assessment.

Significance: Measuring TMT in patients who routinely get early head CTs after severe acute brain injury may capture one component of premorbid frailty.

Research/Grant Support: This research is supported by an NIH-funded training grant to Jonathan Tam (T32HL134615).

DEPARTMENT OF NEUROLOGICAL SURGERY

Abstract 37

TOP 50 MOST INFLUENTIAL ARTICLES ON CERVICAL DEFORMITIES

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Introduction: Cervical deformities encompass a range of structural abnormalities affecting the stability and/or alignment of the cervical spine. These deformities may be caused by congenital malformations, degenerative changes, trauma, or iatrogenic causes. Bibliometric analysis is a useful tool for identifying key studies that have furthered the understanding of cervical deformities as well as how they can be most effectively managed. To date, no study has examined the most influential literature on cervical deformities; thus, the aim of this study is to identify the top 50 works in this field.

Hypothesis: The objective of this study is to identify the 50 most influential articles on cervical spine deformities published between 2000 and 2025 using established citation analysis methods. The hypothesis is that the most influential papers would focus on surgical techniques and long-term patient outcomes.

Methods: A two-step query was conducted on the Clarivate Analytics Web of Science platform to compile the final list of fifty articles. A topic search for "cervical deformity" returned 3,235 results, which were sorted by citation count. Forty-one keywords were generated from the top 100 articles. A second search using these keywords yielded 2,639 results, from which the top fifty most-cited studies were selected. Studies had to focus on cervical spine deformities, including but not limited to cervical kyphosis, inappropriate cervical lordosis, and related surgical interventions.

Results: Of the 2,639 results, fifty were included in the final list based on review of title and abstract. The following information was obtained from the top fifty studies selected: authors, title, article type, total citations, years until first citation, most cited year, years since most cited year, citations in 2025, and average number of citations per year. *Spine* had the highest number of publications, with 14 articles. The *European Spine Journal* had the second-highest number of publications, with 9 articles. *Journal of Neurosurgery: Spine* had the third-highest number of publications, with 7 articles. C.P. Ames had the highest number of publications as a first author, contributing to eight total papers in the top fifty list. The topics covered were surgical techniques and patient outcomes. J.S. Smith had the second-highest number of publications as a first author, contributing to seven total papers in the top fifty list. The topics covered were outcomes and complications. The article with the highest number of citations was by *Scheer et. al.,* with a total of 502 citations. The article with the lowest number of citations in the top fifty was by *Hojo et al.,* with a total of 50 citations. The most recent article was by Lee et al., which was published in 2020 and had 54 citations. The oldest article was by *Harrison et al.,* which was published in 2001 and had 62 citations.

Conclusions: This bibliometric analysis highlights the most influential literature on cervical deformities since the year 2000. Many of the highly cited articles focus on surgical technique as well as long-term outcomes, and complications. By identifying pivotal studies that have influenced current knowledge on cervical deformities, this analysis help guide future directions, clinical practices, and interdisciplinary collaboration.

Abstract 38

SERUM, CSF, AND HIPPOCAMPAL TISSUE NEUROINFLAMMATORY BIOMARKER RESPONSE FOLLOWING TRAUMATIC BRAIN INJURY & CELASTROL ADMINISTRATION

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Introduction: Biomarkers are promising tools for understanding post-traumatic brain injury (TBI) disease pathophysiology, but their biodistribution post-TBI is less understood. Neuroinflammation is a potential TBI therapeutic target. Celastrol, a plant-derived triterpene, has been evaluated in brain disorders but not TBI.

Hypothesis: We hypothesize that experimental TBI elevates neuroinflammatory biomarkers in cerebrospinal fluid (CSF), serum, and ipsilateral hippocampal tissue lysate, and that Celastrol attenuates these changes.

Methods: 24 male Sprague-Dawley rats (275-300g) were separated into four conditions (sham + vehicle, sham + drug, injury + vehicle, injury + drug, (n=6/group)) for biomarker analysis in CSF, serum, and hippocampal tissue lysate 48 hours after injury. Anesthetized rats received a controlled cortical impact (CCI at 6m/s, 2.7 mm depth, 6mm tip diameter, 150 ms dwelling time) injury or sham surgery. A 0.5 mg/kg dose of Celastrol or 0.9% saline (vehicle) was administered 24 and 48h post-CCI. Samples were terminally collected 48h post-injury. Serum, CSF, hippocampal concentrations of biomarkers (IFN-γ, IL-1β, IL-4, IL-5, IL-6, IL-10, IL-13, KC/GRO, TNF-a) were analyzed by MSD multiplex for injury and treatment effects. Differences in biomarker levels between compartments were analyzed by the paired Wilcoxon signed-rank test and between groups of interest by the Mann–Whitney U test.

Results: Vehicle-treated injured groups had significantly elevated hippocampal TNF-α (+529.3%, p=0.010) and reduced IFN-γ (-46.1%, p=0.038) compared to uninjured controls. Celastrol treatment significantly restored hippocampal IFN-γ levels in injured animals (34.52 ± 2.79 μg/ml) compared to uninjured vehicle groups (43.06 ± 7.24 μg/ml; p=0.026) and reduced injury-induced hippocampal TNF-α elevation, though not significantly. Additionally, Celastrol significantly increased serum:hippocampus ratios of IL-6 (p=0.032), KC/GRO (p=0.016), and TNF-α (p=0.016) in injured animals vs. vehicle treatment. Other biomarkers had no injury effects.

Conclusion: This data shows unique multicompartment biomarker changes in response to injury and differential responses to Celastrol.

Significance: To the best of our knowledge, this is the first work characterizing compartmental neuroinflammatory biomarker responses in rats 48 hours after experimental TBI, as well as Celastrol treatment, across serum, CSF, and hippocampal tissue. This data provides an additional line of evidence for future preclinical analysis of potential neuroprotective compounds for TBI.

Research/Grant Support: NIH R21 NS130427

Abstract 39

PREDICTING LONG-TERM SURVIVAL IN HIGH-GRADE GLIOMAS: THE PROGNOSTIC VALUE OF IONM CHANGES AND NEUROLOGICAL DEFICITS

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Introduction: High-grade glioma resection presents challenges in balancing maximal tumor removal with preservation of neurological function. Intraoperative neurophysiological monitoring (IONM) and post-operative neurological deficits (PDs) have each been individually associated with functional outcomes, but their roles as predictors of long-term survival remain unclear.

Hypothesis: We hypothesized that significant intraoperative neurophysiological changes and post-operative neurological deficits are independently associated with decreased long-term survival, and that combined assessment offers enhanced prognostic value.

Methods: We retrospectively analyzed 224 patients who underwent resection of high-grade gliomas with multimodal IONM. Patients were stratified into four groups based on the presence or absence of significant IONM changes and post-operative neurological deficits. Kaplan-Meier survival analysis, log-rank tests, and Cox proportional hazards models were used to evaluate associations between these variables and survival up to 24 months. Adjustments were made for age, preoperative Karnofsky Performance Status (KPS), gender, and baseline neurological deficits.

Results: Patients with IONM changes only had the highest 24-month mortality rate (72.7%), followed by those with both IONM changes and PDs (55.9%). Kaplan-Meier analysis showed significantly worse survival in the IONM-only group compared to patients with neither exposure ($p=0.004$). Adjusted Cox regression revealed that IONM changes alone were independently associated with higher mortality (HR 3.94, 95% CI 1.69–9.21). Adjusted odds of death at 6 months were also highest in this group (OR 4.51, 95% CI 1.17–22.43). Post-operative deficits alone were associated with an increases in mortality risk that did not reach statistical significance in time-specific models.

Conclusions: Significant intraoperative neurophysiological changes are strongly associated with decreased survival following high-grade glioma surgery, even in the absence of post-operative deficits. This may reflect irreversible intraoperative injury or aggressive tumor biology that manifests sub-clinically during surgery but ultimately leads to poor prognosis. Post-operative deficits alone had a weaker, non-significant association with survival.

Significance: IONM changes may serve as early prognostic indicators for long-term survival, providing critical information for intraoperative decision-making and post-operative counseling. These findings support the role of IONM not only in preserving function but also in informing prognosis.

Research/Grant Support: None.

Abstract 40

EX VIVO DIFFUSION TENSOR IMAGING REVEALS CHRONIC NETWORK DISRUPTIONS ACCOMPANYING ENDURING NEUROBEHAVIORAL IMPAIRMENTS IN A PRECLINICAL MODEL OF REPEATED MILD TRAUMATIC BRAIN INJURY

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Introduction: Repeated mild traumatic brain injury (rmTBI) presents challenges for diagnosis and treatment due to the heterogeneous nature and transient clinical presentation. While a negative CT scan is a hallmark of mTBI, diffusion tensor imaging (DTI) and high-definition fiber tractography have emerged as sensitive, non-invasive methods to detect axonal connectivity changes in patients, though *in vivo* DTI in preclinical studies is resolution-limited. Therefore, the current study leverages the high-resolution capabilities of *ex vivo* diffusion tensor imaging and MRI to examine chronic structural connectivity and network-level disruptions throughout the brain in a rat model of rmTBI.

Hypothesis: We hypothesize that whole-brain, high-resolution *ex vivo* DTI reveals chronic structural connectivity and network integrity disruptions 8wks post-rmTBI. DTI-guided immunohistochemistry validates disruptions in regions linked to cognitive deficits, and serum neurofilament light (NfL) levels will be correlated with DTI outcomes.

Methods: Male Sprague Dawley rats (8–10 weeks old) were randomly assigned to receive either dual mild lateral fluid percussion injuries (dFPI, 1.25atm) or dual sham surgeries, 24hrs apart (n=18/group). At 8-weeks post-injury, spatial learning and memory were assessed via the Morris water maze. Following the completion of behavioral testing, rats were euthanized, transcardially perfused, and brains were extracted for DTI imaging followed by graph theory to delineate brain network topology. DTI-guided immunohistochemical analysis of myelin basic protein and serum NfL concentrations were assessed.

Results: At 8 weeks, neurobehavioral assessments showed significant spatial learning and memory deficits (vs. sham, ANOVA, t-tests, p values<0.05). A subgroup (n=6/group) underwent *ex vivo* DTI, revealing dFPI-induced hemispheric differences, including reduced diffusivity in the ipsilateral corpus callosum and ventricular system, with directional diffusivity reduced in the ventricular system. Graph theoretical analysis of DTI connectivity demonstrated dFPI-induced reductions in hippocampal, cortical, and subcortical connectivity (unpaired, two-tailed t-tests, p values<0.05). Hippocampal-seeded analysis showed reduced intra-hippocampal and cortical/subcortical connectivity (p values<0.05). Immunohistochemistry corroborated DTI-identified microstructural changes, including corpus callosum demyelination and accompanying elevated serum NfL.

Conclusion: These findings delineate chronic network disruptions post-rmTBI, underscoring the utility of high-resolution *ex vivo* DTI for mapping connectivity deficits. Integrating *in vivo* imaging and biomarker approaches complements ongoing studies of temporal progression, sex differences, and therapeutic targets post-rmTBI.

Significance: This multi-modal approach aims to address critical gaps in rmTBI diagnosis and prognosis, enhancing our understanding of predictive long-term structural alterations and clinically-relevant serum-based biomarkers for early intervention to mitigate the long-term consequences of repetitive brain injury.

Research/Grant Support: NIH T32HD040686 (EHM), NS124730 (SWC), and Walter L. Copeland Fund (SWC).

Abstract 41

PREDICTORS OF POSTOPERATIVE COURSE AND MORTALITY IN INTRAMEDULLARY SPINAL CORD TUMOR PATIENTS

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Introduction: Intramedullary spinal cord tumors (IMSCTs) are rare, pathologically heterogeneous neoplasms treated by surgical gross total resection. Few studies have comprehensively investigated challenges in postoperative course, from hospitalization to longterm functional recovery, which substantially impact patients' lifespans and quality of life.

Hypothesis: We tested the hypothesis that immediate postoperative neurological deficits were associated with longer hospital stays and lower overall survival.

Methods: Data were retrospectively collected from the medical records of all patients who underwent surgical resection for IMSCTs at a UPMC hospital between January 2002 and December 2020. Predictors included operative complications, cerebrospinal fluid (CSF) leaks, immediate postoperative neurologic deficits, and discharge location, while outcomes included overall survival and length of hospitalization. Adjusted Cox regression models were generated for overall survival and adjusted linear regression models for length of hospitalization. Kaplan-Meier and log rank analyses were used to assess time-to-death differences by neurologic deficit status and discharge location.

Results: Among our 116 patients, a significantly higher proportion of those with neurologic deficits (n=19, 39%) died during the study period compared to those without (n=10, 15%; p=0.003). Neurologic deficits increased the hazard of death by 120% (p<0.001), adjusting for age, pathology, location, extent of resection (EoR), discharge location, and length of hospitalization. Discharge to a specialized care facility was associated with a 4.25 day increase in length of hospitalization compared to discharge home (p<0.001), adjusting for reoperation, postoperative infections, CSF leaks, age, pathology, and EoR. Overall survival differed significantly by neurologic deficit status and discharge location, both separately (p=0.007, p=0.002) and combined (p=0.01).

Conclusions: Intramedullary spinal cord tumor patients are more likely to experience poor outcomes following tumor resection if they have immediate postoperative neurologic deficits. Namely, these deficits make them more likely to experience mortality, longer hospital stays, and subsequent discharge to a specialized care facility instead of home.

Significance: These findings underscore the need for early identification of high-risk patients by immediate postoperative neurologic deficit status, which would enable targeted inpatient management and follow-up strategies. Furthermore, the predictive models generated in this study can be used to inform provider approaches, hospital resource allocation, and patient counseling.

Research/Grant Support: No sources to report.

Abstract 42

HEMOGLOBINOPATHY IS LINKED TO IMMUNE DYSREGULATION AND SYSTEMIC PATHOLOGY FOLLOWING TRAUMATIC BRAIN INJURY: A STUDY OF BERKELEY SICKLE CELL MICE

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Introduction: Hemoglobinopathies, often sickle cell disease (SCD), impact 300+ million individuals globally and their interaction with traumatic brain injury (TBI) remains understudied.

Hypothesis: We hypothesized that the baseline inflammatory state in SCD heightens inflammatory responses, metabolic dysfunction and organ damage following TBI.

Methods: Berkeley SCD and C57BL/6J Wild Type (WT) mice (12-18 weeks, n=6-8 per group) underwent controlled cortical impact (CCI) at 6 m/s, 1.8 mm depth or identical anesthesia without injury (Sham). Tail veins were sampled at baseline, 24h and 72h post-CCI and plasma inflammatory markers quantified via multiplex assays (Meso Scale Discovery, Rockville, MD). Venous blood gas parameters were measured at 48h post-injury. Righting time was assessed immediately post-injury and beam balance evaluated on days 1-3. Organ weights were recorded following sacrifice at 72h. Two-way ANOVA/mixed-effects models assessed group differences.

Results: Four SCD-CCI mice exited the study at 24h-72h due to health deterioration. Genotypic differences (SCD>WT mean concentrations) were identified at baseline in IL-10 ($p<0.0001$), IL-6 ($p=0.0066$), KC/GRO ($p=0.0250$), and TNF-a ($p=0.0003$). At 24h, IL-1B ($p=0.0025$), IL-5 ($p=0.0309$), IL-6 ($p=0.0244$), and KC/GRO ($p=0.0073$) showed SCD>WT difference. IL-1B further demonstrated injury difference (Sham>CCI, $p=0.0143$) at 24h. At 72h, IL-6 ($p=0.0399$) showed WT>SCD difference. Temporally, IL-10 concentrations increased from baseline-24h in WT-CCI ($p=0.0038$) and WT-Sham ($p=0.0232$) groups and from baseline-72h in WT-Shams ($p=0.0323$). In SCD-Shams, IFN-y (24h-72h, $p=0.0346$), IL-1B (baseline-24h, $p=0.0064$), and IL-6 (baseline-24h, $p=0.0274$) increased acutely. SCD-CCI (24h-72h, $p=0.0346$) and SCD-Sham (baseline-72h, $p=0.0375$) groups showed a temporal increase in IL-5. SCD-CCI (baseline-24h, $p=0.0273$), SCD-Sham (baseline-24h, $p=0.0261$) and WT-CCI (baseline-24h, $p=0.0167$) showed an increase in TNF-a over time. From 24h-72h, SCD-CCI mice showed a decrease in TNF-a ($p=0.0364$). PCO_2 was elevated in SCD-CCI vs. SCD-Sham ($p=0.0207$). PO_2 was reduced in SCD-Sham vs. WT-Sham ($p=0.0267$). Righting time was prolonged in SCD-CCI vs. WT-Sham ($p=0.0004$) and SCD-Sham ($p=0.0010$). Beam balance performance was impaired in SCD-CCI vs. SCD-Sham on day 3 ($p=0.0208$). Heart ($p=0.0001$), kidney ($p=0.0328$), and spleen ($p<0.0001$) showed SCD>WT differences in mean weights. CCI decreased mean liver weight in SCD compared to WT mice ($p=0.0426$).

Conclusions: High rates of adverse outcomes, altered inflammatory responses, metabolic derangements in blood gases, worsened motor outcomes, and changes in organ weights collectively suggest multi-system vulnerability in SCD following TBI.

Significance: Hemoglobinopathies may present as ubiquitous risk factors in TBI progression and recovery. Our ongoing studies assessing clinical biomarkers across hemoglobinopathies aim to clarify pathophysiological mechanisms and identify therapeutic targets.

Research/Grant Support: NIH-5R01NS124730 (PI: Shaun Carlson, PhD)

Abstract 43

REAL-TIME CONTINUOUS MICRODIALYSIS FOR MONITORING SPREADING DEPOLARIZATION IN SEVERE TRAUMATIC BRAIN INJURY PATIENTS

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Introduction: Severe traumatic brain injury (sTBI) represents a substantial health crisis and monitoring patients for secondary injury is crucial to initiate timely treatments and improve neurological outcomes. Current intracerebral microdialysis collects microdialysate and uses trajectory analyses with often delayed interpretation. This pilot study aims to characterize detected spreading depolarizations (SDs), defined as potassium transients alongside cerebral glucose levels as a metric of metabolic demand, in patients with sTBI.

Hypothesis: We hypothesize that SD parameters, including slower potassium rise time, will be associated with poorer outcomes in the ICU.

Methods: Participants were enrolled under an IRB-approved protocol (inclusion criteria: >18yo, initial Glasgow Coma Scale (GCS) score of 3−10). Microdialysis catheters were connected to a microfluidic system with integrated electrochemical biosensors to detect potassium and glucose transients in real-time. A novel addition included dexamethasone retrodialysis to prevent gliosis from hindering diffusion. 17 participants were enrolled under an IRB-approved protocol and analyzed (mean age 50±19yrs, 59% male; median GCS 6).

Results: Average monitoring time was 77.35hrs (range 34.5-137.42hrs). We identified 150 SD events in 14/17 participants. There was a significantly slower rise time in the SD-associated potassium transients in patients with ICU mortality compared to survivors ($p<0.05$, Mann Whitney Test). Additionally, we found that patients with normal intracranial pressure (ICP) and partial pressure of oxygen in brain tissue ($PbtO_2$) had significantly faster potassium rise times and durations compared to patients with abnormal ICP and $PbtO_2$ ($p<0.0005$, Mann Whitney test).

Conclusions: Real time neuromonitoring of SDs reveals that increased ICU mortality was associated with slower rise times in SD-associated potassium transients.

Significance: This innovative bedside neuromonitoring technique to detect potassium transients and associated changes in glucose in real-time opens a window of opportunity to identify spreading depolarizations as a potential target for future treatments.

Research/Grant Support: NIH-R01-NS102725 (co-PI Adrian Michael and Ava M. Puccio)

Abstract 44

TOP 50 MOST CITED ARTICLES ON PEDIATRIC CRANIOPHARYNGIOMA

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Introduction: Craniopharyngioma is a rare brain tumor typically seen in children aged 5–14, presenting as cystic, solid, or mixed lesions in the sellar and parasellar regions. As treatment strategies have advanced, so has the literature guiding clinical care. To better understand which studies have most significantly influenced this evolving landscape, citation analysis provides a quantitative lens through which the field's intellectual milestones can be identified and examined. While bibliometric methods have been applied to general pediatric brain tumors, no study has specifically examined pediatric craniopharyngioma. Given the complexity of treatment and long-term quality of life considerations, we aimed to identify the 50 most-cited articles in this field.

Hypothesis: We hypothesized that the most-cited articles would emphasize surgical management and longterm outcomes, reflecting the dual focus on initial intervention and chronic care.

Methods: A two-step literature search was conducted using the Thomson Reuters Web of Science database to identify the 50 most-cited articles on pediatric craniopharyngioma published between 1945 and 2024. Articles were included if they focused primarily on pediatric craniopharyngioma, including its diagnosis, treatment, or outcomes, and excluded if they featured non-human studies and non-English publications. An initial Boolean query yielded 1,202 results, from which 50 keywords were derived to inform a second search. This returned 1,183 articles, from which the 50 most-cited articles were selected. For each, we recorded citation metrics and publication details.

Results: The top 50 articles had citation counts ranging from 86 to 464 (mean 154 ± 76). The most cited was by Bunin GR (464 citations), with publications spanning 1980 to 2019. The decade between 2000–2010 was the most productive with 26 articles, while the 2010s had the most total citations (3,676). The most cited year overall was 2023 (543 citations). Articles appeared across 22 journals, with *Child's Nervous System*, *JCEM*, and *IJROBP* contributing eight articles each. H.L. Müller was the most prolific author, with 13 first-author publications. The article topics primarily focused on epidemiology/classification and surgical management (n = 11 each, 22%), followed by obesity and quality of life (n = 9, 18%), radiation therapy (n = 9, 18%), and institutional experiences (n = 6, 12%).

Conclusions: This bibliometric analysis highlights the most influential literature on pediatric craniopharyngioma over the past several decades. The majority of highly cited articles focus on surgical management, radiation therapy, and long-term outcomes and quality of life.

Significance: Understanding which studies have shaped current knowledge can inform future research priorities, clinical guidelines, and interdisciplinary collaboration. This analysis provides a framework for clinicians, researchers, and trainees to identify landmark studies and key contributors in pediatric craniopharyngioma, ultimately guiding evidence-based practice and fostering more targeted scientific inquiry.

Abstract 45

EVALUATION OF BRAIN-DERIVED TAU AS A SERUM BIOMARKER OF ACUTE SEVERE TRAUMATIC BRAIN INJURY

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Introduction: Brain-derived (BD) Tau is an emerging neurodegenerative marker that recognizes Tau isoforms expressed exclusively in the brain and has yet to be examined extensively in severe traumatic brain injury (sTBI). In the sole study in TBI, serum BD-Tau outperformed total and phosphorylated Tau in evaluating injury status and clinical outcomes in 39 subjects.

Hypothesis: This goal of this study was to examine BD-Tau temporal trajectory in serum of acute sTBI to identify novel biomarker signatures of injury and outcome.

Methods: Under IRB approved protocols, serial serum samples (0-9 days post-injury) were collected from sTBI patients. BD-Tau was measured using the Simoa-Quanterix platform, using the TauJ.5H3 antibody, designed to selectively bind to continuous exon 4–5 sequences on CNS-derived tau isoforms and avoids the exon 4a region predominantly expressed in peripheral tissues. Statistical analysis included group comparisons and linear regression models of time, age, sex and outcome.

Results: 283 participants (1941 samples) were analyzed (median initial GCS 7, mean age 42.7±19.0, 78.1% male). Using 12-hour time-intervals, linear regression (time*time) showed a 'U-shape' temporal profile ($p<0.0001$). BD-Tau expression at 156-hours post-injury was significantly higher in patients with a favorable 6-month outcome compared to poor outcome ($p=0.046$). At 12-, 36- and 132-hours post-injury, females had higher BD-tau expression than males ($p=0.042$, 0.027 and 0.015). At 108-, 120- and 144-hours post-injury, older patients had higher BD-tau expression than younger patients ($p=0.025$, 0.026 and 0.034). Linear regression showed no significant association of sex, age and outcome when controlled for covariates.

Conclusions: This is the most comprehensive assessment of BD-Tau in TBI to date demonstrating a temporal profile distinct from other hallmark brain injury fluid biomarkers. Individual time-points show differences across age, sex and outcome.

Significance: Future work aims at characterizing patient BD-Tau trajectories with secondary injury parameters to uncover novel prognostic indicators. Elucidating BD-Tau as an sTBI biomarker serves to provide valuable insights into mechanisms of neuronal damage.

Research/Grant Support: T32HD040686 (PI: Sarah E. Svirsky), P50NS30318 (PI: Ava M. Puccio)

DEPARTMENT OF PHYSICAL MEDICINE AND REHABILITATION

Abstract 46

ADULT HYPERTENSION AS A CLINICALLY-RELEVANT COMORBIDITY AUGMENTING NEUROBEHAVIORAL DEFICITS AND PATHOLOGICAL OUTCOMES AFTER PEDIATRIC TRAUMATIC BRAIN INJURY

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Introduction: About 500,000 yearly emergency-room visits are due to childhood traumatic brain injury (TBI), which may render cognitive and emotional sequelae. Half of adults are diagnosed with hypertension, due to diet, obesity, smoking, or genetic factors, which causes cardiovascular complications. Pediatric TBI prior to developing a comorbidity like hypertension has not been investigated.

Hypothesis: We hypothesized that hypertensive rats will perform inferiorly post-injury to normotensive rats.

Methods: Spontaneously Hypertensive (SHR) and normotensive Wistar male rats received either a moderate, right-parietal controlled cortical impact (CCI) or a sham injury at postnatal day 17. Four adulthood tasks measured post-TBI neurobehaviors after hypertension becomes expressed: the 3-Choice serial reaction time test (3-CSRT, sustained attention) at 4 months post-pediatric TBI, T-maze attentional set-shifting (behavioral flexibility), open field testing (OFT, anxiety), and the shock-probe defensive burying test (SPDB, active and passive coping). Lesion and bilateral ventricle volumes were assessed.

Results: TBI rats required more training sessions on 3-CSRT, with normotensive TBI rats displaying lower performance accuracy and higher omissions, while hypertensive rats also displaying enhanced distractibility ($p<0.05$). SHR-TBI rats showed impaired rule learning on T maze and set-shifting deficits when rule required a left arm turn, indicative of perceptual-attentional spatial neglect ($p<0.05$). SHR-TBI rats engaged in greater active avoidance times in the SPDB ($p<0.05$), indicative of increased anxiety, while no differences were detected in OFT ($p>0.05$). Hypertension enlarged lateral ventricles, while injury further enlarged ipsilateral ventricle regardless of tensive status ($p<0.05$).

Conclusions: Rats exhibiting the hypertensive phenotype during adulthood exhibited more pronounced attentional and emotional alterations post-injury compared to normotensive injured rats, as well as the largest ventricle volumes.

Significance: These results support using hypertensive rats to further enhance bench to bedside translatability and refine therapeutic approaches.

Research/Grant Support: NIH NS110609 (and Landis Award for Outstanding Mentorship), NS137253, Interdisciplinary Neuroscience Award - Children's Hospital of Pittsburgh (PI: Corina O. Bondi, PhD), UPMC Children's Research Advisor Committee Dissertation Fellowship (PI: Eleni H. Moschonas, PhD), and NS084967, NS121037 (PI: Anthony E. Kline, PhD).

Abstract 47

INTERACTIONS OF HYPERTENSION AND ADULT TRAUMATIC BRAIN INJURY ON COGNITION, ANXIETY, AND PATHOLOGICAL OUTCOMES IN RATS

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Introduction: Approximately 2.8 million people sustain a traumatic brain injury (TBI) yearly in the United States. Many patients endure cognitive and psychopathological consequences. Assessing complex attention deficits post-TBI, especially in conjunction with overlapping comorbidities, is timely and necessary. An estimated 50% of adults have hypertension, which can precipitate cardiovascular disease, strokes, and premature death. We aimed to investigate, for the first time, how hypertension can affect TBI-related neurological, physiological, and cognitive impairments in adult rats.

Hypothesis: We hypothesized that hypertensive rats will perform worse post-injury than normotensive rats.

Methods: Spontaneously Hypertensive (SHR) and normotensive Wistar male rats received a moderate, right-parietal controlled cortical impact (CCI) or a sham injury at four months of age. SHR-TBI rats exhibit 10% higher heart rate and 30% higher arterial pressure than normotensive-TBI counterparts. Moreover, SHR-TBI rats display impaired beam-walking and spatial learning compared to SHR shams ($p<0.05$). Four new tasks measured post-TBI neurobehaviors: the 3-Choice serial reaction time test (3-CSRT, sustained attention), T-maze attentional set-shifting (behavioral flexibility), open field testing (OFT, anxiety), and the shock-probe defensive burying test (SPDB, active/passive coping).

Results: All TBI rats displayed lower accuracy and higher omissions on 3-CSRT, with SHR-TBI rats demonstrating the most pronounced attentional impairments, as well as higher premature responses versus all groups, indicative of impulsivity ($p<0.05$). SHR-TBI rats also spent less time approaching and actively burying the shock probe in SPDB ($p<0.05$). Analyses of cortical lesions, bilateral ventricle volumes, brain water weight, and serum inflammatory markers are ongoing.

Conclusions: Receiving a moderate-severity CCI during adulthood, while exhibiting high blood pressure, rendered adult male rats to perform worse on a complex attentional task compared to either injury or hypertension-alone groups, particularly on percent accuracy and impulsivity measures.

Significance: Understanding the impact of underlying conditions such as hypertension on TBI pre-clinically is critical to further developing clinically-relevant therapies.

Research/Grant Support: NIH NS110609 (and Landis Award for Outstanding Mentorship), NS137253, Interdisciplinary Neuroscience Award - Children's Hospital of Pittsburgh (PI: Corina O. Bondi, PhD), UPMC Children's Research Advisor Committee Dissertation Fellowship (PI: Eleni H. Moschonas, PhD), and NS084967, NS121037 (PI: Anthony E. Kline, PhD).

Abstract 48

NEUROBEHAVIORAL OUTCOMES AFTER SEVERE CONTROLLED CORTICAL IMPACT (CCI) INJURY IN MALE AND FEMALE MICE

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Introduction: TBI can chronically disrupt the neuroendocrine axis, which may be associated with psychological health disorders. However, sex-specific outcomes and their underlying disruptions are not well understood.

Hypothesis: We examined sex-specific injury effects on behavior in the chronic phase post-TBI.

Methods: Adult male and female mice (n=47/sex) received controlled cortical impact (CCI, 6.0±0.2 m/s, 2mm depth) or sham. Behavior assays assessed anxiety [open field (OF), 7 days post-injury (dpi)], zero maze (EZM, 11dpi), sociability (SI, 15dpi)], anhedonia [sucrose splash (SST, 17dpi)], fear learning/memory [conditioning/extinction (FC/FE, 21–23dpi)], and general activity. Data were analyzed via two-way ANOVA followed by Tukey's multiple comparisons.

Results: CCI induced hyperactivity: CCI increased activity in OF and SI and increased open zone time in EZM. CCI increased anxiety-like behaviors: CCI reduced center zone activity in OF and increased corner zone time during SI. CCI disinhibited social behaviors: CCI decreased SI interaction visits. Anhedonia and some anxiety behaviors had sex-specific effects: Females groomed less in SST and spent less time in OF center zone. Fear learning was influenced by injury and/or sex. In fear learning (FC), CCI decreased freezing time and increased freezing latency, with females showing a greater reduction. CCI impaired fear memory (FE): CCI decreased freezing time. There was a sex-specific effect on stress-induced plasma corticosterone levels: CCI decreased 23dpi corticosterone in males but not females.

Conclusion: Overall, CCI induced psychological health phenotypes, with sex-specific differences in behavior outcomes and neuroendocrine outputs.

Significance: Ongoing work will explore the impact of injury across the neuroendocrine axis, correlating this with behavior to better understand sex-specific injury outcomes.

Research/Grant Support: Department of Defense (Award Number: W81XWH-22-2-0056) from the Department of Defense (DoD) Congressionally Directed Medical Research Program (CDMRP)

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Abstract 49

AQUA THERAPY AS A BRIDGE FOR ENVIRONMENTAL ENRICHMENT TO RECOVER NEUROBEHAVIOR AFTER TRAUMATIC BRAIN INJURY

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Introduction: Environmental enrichment (EE) facilitates neurobehavioral recovery after traumatic brain injury (TBI) in both sexes and all age groups. While EE is typically introduced immediately and continuously after TBI, this approach is not practical in clinical settings, where rehabilitation generally starts after the critical care phase. Additionally, rehabilitation often occurs for just a few hours each day. Given the critical role of early intervention in recovery, this study sought to examine the use of aqua therapy (swimming) as a preliminary treatment before commencing EE.

Hypothesis: Bridging EE with aqua therapy will enhance neurobehavioral benefits beyond that of EE alone.

Methods: Anesthetized adult male rats received a controlled cortical impact of moderate severity (2.8 mm impact at 4 m/s) or sham injury. Rats were housed in standard (STD) conditions for one week during which time they were provided free access to a water maze to swim for 90 s with no goal of platform seeking (i.e., simply exercise). EE (4-hr/day) began on day 8 for the bridge and continuous EE groups. Motor (beam-walk/balance) and cognitive (water maze) performance was evaluated on days 8-12 and 14-20, respectively. The data were analyzed by repeated measures analysis of variance (rmANOVAs) and Newman-Keuls post-hoc tests.

Results: Bridging EE with aqua therapy facilitated motor recovery, spatial learning, and memory retention vs. non-treated STD-housed rats ($p<0.05$) but did not show additional benefits over EE alone ($p>0.05$). Between the STD-housed rats, those that received aqua therapy performed better on both tasks vs. those in the STD-only group ($p<0.05$).

Conclusions and Significance: While bridging EE with aqua therapy did not provide additional benefits as hypothesized, the observed neurobehavioral improvements in STD-housed rats following a relatively mild early therapy are promising and underscore the potential value of early rehabilitative interventions following TBI.

Research/Grant Support: Supported by NIH NS084967 and NS121037 (AEK).

Abstract 50

TEMPORAL PATTERNS OF CYTOKINES THROUGHOUT THE ACUTE AND CHRONIC RECOVERY PERIOD AFTER SEVERE TRAUMATIC BRAIN INJURY IN MICE

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Introduction: The mechanistic impacts of patterns and temporal profiles of neuro-inflammatory signaling are poorly understood, although associated with increased secondary pathology as well as worse clinical outcomes after traumatic brain injury (TBI). It is critical to characterize these inflammatory patterns and profiles among male and female mice in a contusion model of experimental TBI. We investigated temporal inflammatory cytokine profiles after severe TBI.

Hypothesis: We hypothesize that severe TBI will increase brain levels of proinflammatory cytokines and temporal patterns will be analyte specific.

Methods: Adult male and female C57BL/6J mice (n= 8-15/group) received severe controlled cortical impact (CCI, 6.0±0.2m/s, 2mm depth) or sham (anesthesia only). Tissue was collected 1-day post-injury (dpi), 3dpi, 7dpi or 23dpi. Cytokine levels were measured using the Mesoscale Discovery Assay (V-PLEX Mouse Cytokine 19-Plex) in the ipsilateral hemisphere to the impact. Data were analyzed using a two-way ANOVA followed by Tukey's multiple comparisons.

Results: There were no CCI effects on several cytokines including interleukin (IL)-5, IL-9, IL-10, and IL-15. Other cytokines remained elevated across all dpi versus sham, with peak levels occurring at various timepoints. IL-1β was consistently increased after CCI across all dpi. Monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α, MIP-2, IL-6 and keratinocyte attractant/growth-regulated oncogene (KC/GRO) peaked at 1dpi in response to CCI and remained increased across all dpi. However, IL-33 and interferon gamma-induced protein (IP)-10 peaked at later timepoints – 7 or 23 dpi – after CCI, however, were increased across all dpi.

Conclusions: We identified unique temporal patterns of key cytokines. Chemokines, which play a role in mediating cellular immunity, are elevated after CCI. Ongoing work aims to understand trends of peripheral cytokine levels and expand to other biomarkers, such as soluble receptors.

Significance: Understanding temporal patterns of these biomarkers will help guide targeted intervention strategies.

Research/Grant Support: Department of Defense (Award Number: W81XWH-22-2-0056) from the Department of Defense (DoD) Congressionally Directed Medical Research Program (CDMRP)

Abstract 51

RESCUING NEUROBEHAVIORAL CAPABILITY IN AGED RATS USING A COMBINED THERAPY OF NICOTINIC ACETYLCHOLINE RECEPTOR ALLOSTERIC MODULATION AND ENVIRONMENTAL ENRICHMENT AFTER EXPERIMENTAL BRAIN TRAUMA

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Introduction: Traumatic brain injury (TBI) is a leading cause of death and disability and poses significant challenges for elderly populations, often exacerbating existing age-related cognitive decline. Empirical evidence suggests disruptions in cholinergic neurotransmission following TBI may contribute to cognitive deficits. Therapies that enhance acetylcholine (ACh) transmission may ameliorate cognition, especially in conjunction with noninvasive rehabilitation, which is akin to the real world. We demonstrated that a parietal TBI induces attentional deficits in young adult rats, males and females.

Hypothesis: We hypothesized that parietal injury in aged (15-16 months) male rats will augment attention impairments and that chronic NS-1738, a modulator of the α7-nicotinic ACh receptor (α7-NAChR), will improve behaviors post-TBI, alone and combined with environmental enrichment (EE).

Methods: Aged male rats were trained in the 3-choice serial reaction time task (3-CSRT) prior to a right parietal moderate controlled cortical impact (CCI) or sham injury. They required more sessions to train than young adults ($p<0.05$). On post-injury day (PID) 1, rats were randomized to daily NS-1738 (5 mg/kg) or vehicle, and daily EE (24h) or standard housing. 3-CSRT retrials occurred on PID 17-27. Statistical analysis utilized repeated measures ANOVAs with Newman-Keuls post-hoc tests. Anxiety-like behavior was assessed by open field test (OFT) on PID 28.

Results: TBI-induced cognitive deficits were pronounced in aged rats ($p<0.05$) and were rescued by chronic NS-1738 ($p<0.05$). Moreover, NS-1738+EE rendered an additive effect on raising accuracy and lowering omissions ($p<0.05$). TBI reduced OFT center exploration without altering ambulation ($p<0.05$). NS-1738 and EE individually restored center exploration, suggestive of ameliorating anxiety ($p<0.05$). NS-1738+EE partially restored hippocampal cell counts without promoting cortical tissue preservation. Ongoing analyses include serum inflammatory markers and choline acetyltransferase quantification in the basal forebrain.

Conclusions: The combined NS-1738 and EE housing therapy was most effective at restoring attentional behavior compared to therapies administered alone, while also partially restoring hippocampal cell survival counts without being effective at reducing the extent of the cortical cavitation.

Significance: These findings support benefits of α7-NAChR modulation and/or enrichment housing therapy after brain trauma in aged animals.

Research/Grant Support: NIH NS110609 (and Landis Award for Outstanding Mentorship), NS137253 (PI: Corina O. Bondi, PhD), UPMC Children's Research Advisor Committee Dissertation Fellowship (PI: Eleni H. Moschonas, PhD), and NS084967, NS121037 (PI: Anthony E. Kline, PhD).

Abstract 52

BRIDGING ENVIRONMENTAL ENRICHMENT WITH AMANTADINE TO PROMOTE NEUROBEHAVIORAL RECOVERY AFTER PEDIATRIC TRAUMATIC BRAIN INJURY

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Introduction: Environmental enrichment (EE) accelerates motor and spatial learning after traumatic brain injury (TBI), with benefits observed across different sex and age groups. While EE is typically introduced immediately after TBI, this approach is not clinically feasible, as rehabilitation often begins post-critical care. Given the importance of early intervention for recovery, this study explored the potential of amantadine (AMT) as a bridge therapy prior to EE. AMT was chosen based on preclinical and clinical evidence supporting its use in adult TBI, suggesting it may also be effective for pediatric TBI.

Hypothesis: Bridging EE with AMT will increase motor and cognitive benefits beyond that of EE alone.

Methods: Anesthetized post-natal day 21 male rats received a cortical impact of moderate severity (2.5 mm impact) or sham injury. Rats were housed in standard (STD) conditions for one week and administered either AMT (10 mg/kg) or saline vehicle (1 mL/kg) intraperitoneally for 7 days. EE (6-hr/day) began on day 8 for the bridge and continuous EE groups. Motor and cognitive performance was assessed on days 8-12 and 14-21, respectively. The data were analyzed by repeated measures analysis of variance and Newman-Keuls post-hoc.

Results: Bridging EE with AMT facilitated motor recovery and acquisition of spatial learning and memory vs. vehicle-treated STD-housed rats ($p<0.05$) but did not provide additional benefits over EE alone ($p>0.05$), which does not support the hypothesis. Between the STD-housed rats, the AMT-treated group performed better on both tasks vs. the STD-only group ($p<0.05$).

Conclusions and Significance: Bridging EE with AMT did not provide additional benefits, but the improvements in STD-housed rats following a short-term pharmacotherapy early after TBI are promising and underscore the potential value of early rehabilitative interventions following TBI. The lack of an additive effect may be due to a sub-optimal dose of AMT and thus a dose response study is warranted.

Research/Grant Support: Supported by NIH NS084967 and NS121037 (AEK)

Abstract 53

EVALUATING COGNITIVE PERFORMANCE USING THE NIH TOOLBOX COGNITIVE BATTERY FOLLOWING PEDIATRIC TRAUMATIC BRAIN INJURY (TBI)

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Introduction: Up to 50% of children with TBI experience lasting cognitive impairment. This study evaluates the NIH Toolbox Cognitive Battery (NIH TB-CB) as an accessible tool for evaluating cognition in children with TBI.

Hypothesis: We hypothesized that children with TBI would score lower on the NIH TB-CB compared to those with orthopedic injuries (OI) and that severe TBI would be associated with greater cognitive deficits than complicated mild-to-moderate TBI.

Methods: We analyzed data from 180 children (ages 3-18) hospitalized overnight at UPMC Children's Hospital of Pittsburgh with a complicated mild to severe TBI (Glasgow Coma Scale [GCS] of 3-12 or 13-15 with intracranial injury; n=120) or OI (n=60). Cognitive function was assessed using the NIH TB-CB composite scores for Fluid, Crystallized, and Total Cognition. Linear mixed models examined associations between injury group, timepoint, and their interaction, adjusting for sex and socioeconomic status (SES). All p-values were evaluated using a Bonferroni-corrected significance threshold of $\alpha=0.017$.

Results: Injury group or its interaction with timepoint was not significantly associated with Total, Fluid, or Crystallized Cognition, though Fluid Cognition improved from 6 to 12 months post-injury across both injury groups ($p=0.005$, $d=0.19$). SES was positively associated with all cognition scores ($p<0.001$). Individual NIH TB-CB subtests were not significantly associated with injury group or its interaction with timepoint ($p>0.017$). Children with severe TBI performed significantly worse on Total and Fluid Cognition at 6 months (Total: $p=0.012$, partial $\eta2=0.03$; Fluid: $p=0.004$, partial $\eta2=0.06$) and 12 months (Total: $p=0.002$, partial $\eta2=0.06$; Fluid: $p<0.001$, partial $\eta2=0.11$) than children with complicated mild-moderate TBI.

Conclusions: The NIH TB-CB detects poorer cognitive performance in children with severe TBI at 6 and 12 months post-injury, particularly in Fluid Cognition.

Significance: These findings support using the NIH TB-CB to track cognitive recovery in children with TBI, especially in resource-limited settings.

Research/Grant Support: NICHD K01HD097030 (PI: Treble-Barna), NICHD T32HD040686 (PI: Kochanek)

The Safar Center for Resuscitation Research gratefully acknowledges the support of our sponsors:

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