Notch1 Signaling in Neuroblastoma Tumor Vasculature after High-Dose Radiation Therapy

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INTRODUCTION: Use of high-dose radiation therapy (HDRT) in neuroblastoma is limited. Notch signaling, which regulates vessel formation, maintenance, and stabilization, plays a role in neuroblastoma cell lines. However, its role in vascular response to HDRT is unknown. Our aim is to investigate how Notch signaling regulates the effect of HDRT on the neuroblastoma tumor vasculature.

METHODS: Human NGP neuroblastoma tumor cells were implanted into the left kidney of nude mice to form xenograft tumors. Tumors were subjected to O Gy, 2 Gy, and 12 Gy HDRT. Total RNA was harvested 6 and 72 hours later. Paraffin sections were co-immunostained with antibodies against Notch components Notch1, DLL4, JAGGED-1, and endomucin. HUVEC monolayers were also treated with intervals of HDRT. RTPCR was performed using gene specific primers for Notch receptors; Notch1, Notch2, Notch3, Notch ligands DLL4, JAG1, and target genes Hey1 and Hey2.

RESULTS: Increased Notch1 coinciding with endomucin immunostaining was observed in NGP tumors at 72 hours after 12 Gy HDRT. JAG1 was increased in endomucin (+) endothelial cells of tumor vessels. To confirm the effect of HDRT, we examined the change in Notch receptors, ligands, and signaling in response to high-dose irradiation in human umbilical vein endothelial *cells* in monolayer. As early as 6 hours after irradiation with doses >8 Gy, there was increased Notch1, JAG1, and increased Notch signaling, as indicated by increased HEY1 and HEY2 (Figure).

CONCLUSIONS: Increased expression of Notch1 and its targets in tumor endothelial cells occurred in response to HDRT. Therefore, HDRT is a potentially effective treatment for neuroblastoma by disturbing its vasculature.

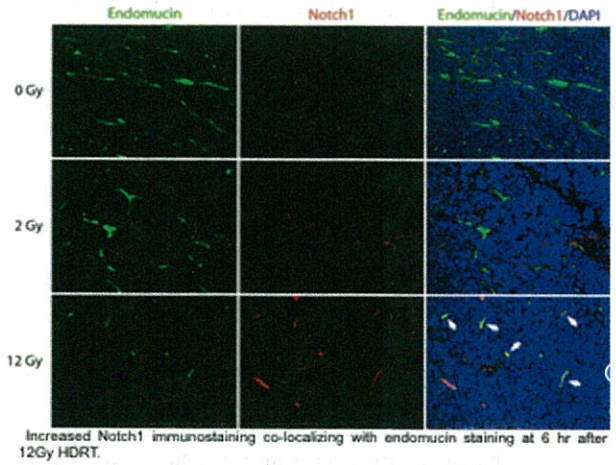

Figure.

Parenteral Nutrition Use in Pediatric Traumatic Brain Injury Patients Is Associated with More Frequent Complications: A Propensity-Matched Analysis Using the National Trauma Data Bank

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INTRODUCTION: Early nutritional support for children with traumatic brain injury (TBI) has been associated with lower mortality, but the specific impact of parenteral nutrition (PN) in this population is not known. Early PN has not been shown to improve mortality in pediatric ICU patients and in adult trauma patients, but has been associated with more frequent complications. We hypothesized that the use of PN after pediatric TBI is associated with higher mortality and more frequent complications.

METHODS: Data from the National Trauma Data Bank (2007 to 2015) were used to obtain a retrospective cohort of children (<15 years old) with TBI. Propensity-score matching (1:3) was used to control for potential treatment bias related to PN use. The matched cohort was used to compare outcomes and complications between patients receiving or not receiving PN. Due to covariate imbalance in Glasgow Coma Scale and laparotomy status after matching, additional adjustment was applied.

RESULTS: Among 27,636 children with TBI, 631 received PN. The median time to PN initiation was 3 days, with 25% of patients having PN initiated on the first hospital day. Propensity-score matching identified 578 PN patients and 1,734 controls. After adjustment, PN use was not associated with increased mortality, but was associated with longer hospital stay and more complications.

CONCLUSIONS: Initiation of PN in pediatric TBI patients frequently occurs before 3 days and is associated with longer hospital stay and more complications. The potential benefit of early nutritional support should be balanced with the risk of complications from parenteral delivery. (Support: grants from the National Center for Advancing Translational Science of the US NIH. KL2TR001854, UL1TR001855, and UL1TR000130.)

Patterns of Pediatric Mortality from Motor Vehicle Crashes among US Counties: Where Are the Disparities?

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INTRODUCTION: Motor vehicle crashes (MVCs) are a significant and preventable cause of death in children. Previous studies showed variability in pediatric MVC mortality among states in the US. To guide resources appropriately, a more detailed evaluation of pediatric mortality is imperative. In this study, we sought to evaluate the patterns of disparities in pediatric mortality from MVCs at the county level.

METHODS: We used deidentified deaths from MVCs in the Fatality Analysis Reporting System for years 2010 to 2015. MVC deaths were defined as crashes on US public roads resulting in a death within 30 days. Children younger than 15 years were included. We used a spatial Bayesian hierarchical Poisson model to estimate annual county-level MVC mortality.

RESULTS: A total of 31,747 MVC deaths in children were recorded. The average age was 7 years (SD 4). The mean crude annual mortality was 1.4 (SD 1.7) deaths per 100,000 children. Estimated mortality ranged between 0.1 (95% CI 0.0−0.2) deaths per 100,000 in Suffolk county in Massachusetts and 13.8 (95% CI, 10.1−18.2) deaths per 100,000 in La Paz county, Arizona. Among counties with more than 100,000 children, Texas, Arizona, and Louisiana had the most counties with very high mortality rates; counties in the Northeast, in California, and along the Great Lakes had the lowest mortality rates (Figure).

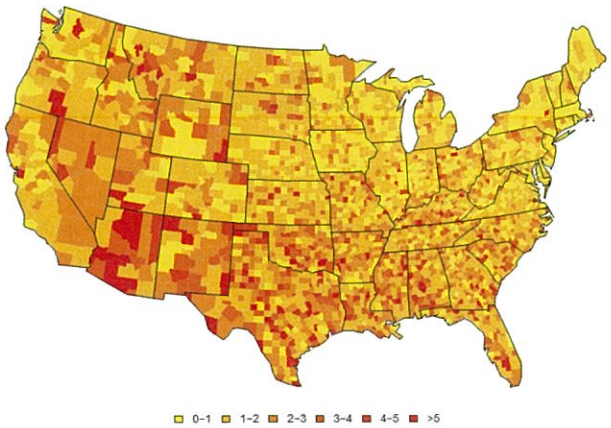

Figure. Estimated county-specific annual motor vehicle crashe deaths per 100,000 children in the US.

CONCLUSIONS: Pediatric mortality from MVCs varied dramatically within states. Our findings will be instrumental to direct state resources toward areas with excessive pediatric MVC deaths.

Pediatric Resuscitation: Weight-Based Packed Red Blood Cell Volume Is a Reliable Predictor of Mortality

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INTRODUCTION: Military data have demonstrated that a threshold of 40 mL/kg of all blood products in the first 24 hours reliably predicts early and in-hospital mortality. We sought to define massive transfusion (MT) cutoff based on packed red blood cells (pRBCs) per volume in the civilian pediatric trauma setting.

METHODS: We performed a 3-year review (2014 to 2016) of the pediatric-TQIP database. We included all pediatric patients aged 4 to 18 years who received any blood product after trauma. Transfusion outcomes were evaluated based on weight-based volume of pRBCs and total-blood products transfused $\leq$ 24 hours of admission. Area under the curve of the receiver operating characteristic (AUROC) curve analysis was performed.

RESULTS: A total of 93,350 patients were analyzed, of whom 1,495 were included in our study. Mean age was 13±4 years, and median Injury Severity Score (ISS) was 26 (range 17 to 35). Sensitivity and specificity for 24-hour mortality were optimal at 20 mL/Kg pRBCs volume in the first 24 hours. Compared with 40 mL/kg total blood products volume, 20 mL/kg pRBCs volume achieved higher discriminatory power for predicting 24-hour morality (AUROC: 0.781 vs 0.672, p<0.001) (Figure).With the use of a threshold of 20 mL/kg, patients were divided into MT (n=553) and no-MT (n=942). Patients who received MT had higher ISS (p<0.001), were more likely to receive mechanical ventilation (p<0.001) and ICU admission (p<0.001), and had a higher 24-hour mortality rate (23.1% vs 7.6%, p<0.001). On regression analysis, MT was independently associated with increased 24-hour mortality (odds ratio 3.8, 95% CI 2.4−4.7).

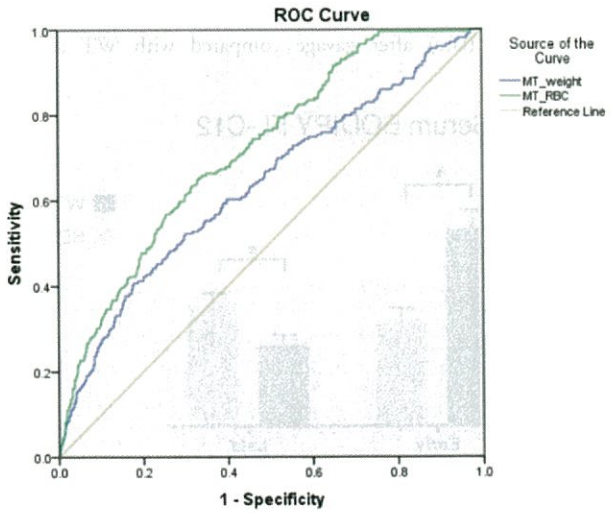

Figure. Twenty-four−hour mortality receiver operating characteristic (ROC) curve.

CONCLUSIONS: In civilian setting, the use of weight-based pRBCs volume among pediatric patients is a better predictor of 24-hour mortality compared with weight-based total blood products volume. These results shall provide a consistent framework for MT protocol development in pediatric resuscitation.