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CLiPPs

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CLiPPs (**C**urrent **L**iterature in **P**ediatric **P**sychosomatics) *is a pertinent article review through the AACAP Physically Ill Child Committee for psychosomatic clinicians from a range of medical science journals and literature. We are very excited for our inaugural issue is finally here and have already begun working on our Summer 2016 edition.*

I hope you enjoy this ICU/delirium themed issue. Herein, we'll likely all learn something new, as well as find greater literature to support our collective expert opinions. There are many inroads being made in pediatrics delirium and pediatric ICU psychiatry, and two of the papers reviewed in this issue exhibit this well. The two other papers reviewed here showcase how adult literature can both help answer some of our nagging clinical questions while also making us cautious with our extrapolations and leaving us wanting more. As is seen in any good research, readers are left with more understanding of what we do and do not know. Let these papers and their reviews lead us to ask better questions, further refine our assumptions, think more critically, and lead to more robust research. Lastly, we are pleased to have our first fellow and supervising attending duo review an article. Cheers!

Delirium and Mortality in Critically Ill Children: Epidemiology and Outcomes of Pediatric Delirium

Background and Objective: Delirium is associated with increased mortality and prolonged, complex hospital stays. The natural history of pediatric delirium is not well described in the literature. This study assessed all admissions to a PICU over a single year for delirium and described the cohort in detail. Goals were to determine frequency, incidence, time to onset, duration, fluctuation of clinical manifestations, phenotype, associated risk factors, and effect on hospital outcome measures including mortality, length of stay, duration of mechanical ventilation (MV).

Methods: All patients admitted to the PICU for a year (9/1/14 – 8/31/15) were screened twice daily for delirium using the CAPD. Any developmentally delayed (DD) child with positive screen had subsequent clinical evaluation. Patients were described daily as 'comatose', 'delirious', 'normal' or 'unknown'. Time in PICU to onset, overall duration and recurrence of delirium were tracked. Subtypes were categorized using the RASS, and demographics were collected including age, sex, primary diagnosis, pre-existing medical conditions, illness severity as measured by Pediatric Index of Mortality-3, and developmental status. The Pediatric Logistic Organ Dysfunction 2 (PELOD-2) score, after excluding the neurologic component, need for respiratory support, and exposure to medications by category, was collected daily. After hospital discharge mortality, duration of MV, PICU length of stay

and hospital length of stay were collected as well.

Results: 1547 admissions were screened. Incidence of delirium was 17.3%, prevalence was 16.6%. Independent predictors of delirium included very young age (2 years or less), DD, high illness severity, MV, coma, and administration of benzodiazepines and anticholinergics. Adjusted odds of delirium diagnosis were 5X greater in patients who received benzodiazepines. Phenotypes were most often hypoactive (46.4%) or mixed (45.2%). PELOD scores were higher on delirious days, even with neurologic component being ignored. PICU LOS was more than 2X longer, and overall hospital LOS was longer. Duration of MV and a 5X higher in-hospital mortality rate were associated with delirium.

Conclusions: Delirium occurs frequently in critically ill pediatric patients and is associated with poor outcomes. Risk factors include young age, DD, and high severity of illness. Modifiable risk factors include deep sedation and receiving benzodiazepines and anticholinergics. Hypoactive and mixed subtypes were more common in this cohort, may have a worse prognosis, and are more likely to be missed without routine screening. Finally, delirium was 5X more common in patients exposed to benzodiazepines. This association requires further assessment. Detailed assessment of exposure is needed to accurately assess probability of potentiating delirium with benzodiazepine use.

Take Away: Incidence of pediatric delirium in patients admitted to a PICU over a single year is high (17.3%). Several risk factors are modifiable. Studies on intervention are needed to determine best practices to limit delirium exposure in at risk children.

References:

1. Smith HA, Brink E, Fuchs DC, et al. Pediatric Delirium: Monitoring and management in the pediatric intensive care unit. Pediatr Clin North Am 2013; 60:741-760.
2. Schieveld JN, Leentjens AF. Delirium in severely ill young children in the pediatric intensive care unit (PICU). J Am Acad Child Adolesc Psychiatry 2005; 44:392-394; discussion 395.
3. Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion and delirium screening practices in the care of mechanically ventilated children: a wake-up call for the pediatric critical care community. Crit Care Med 2014; 42(7): 1592-600.

Reviewer: Julienne Jacobson, MD, USC/Children's Hospital Los Angeles, Los Angeles CA.

Source: Delirium and Mortality in Critically Ill Children: Epidemiology and Outcomes of Pediatric Delirium. Traube C, Silver G, Gerber LM, Kaur S, Mauer EA, Kerson A, Joyce C, Greenwald BM. Crit Care Med. 2017; 45(5):891-898. Link here.

Clonidine for Sedation in the Critically Ill

Background and Objective: Typical sedatives for invasive mechanical ventilation (IMV) are propofol, benzodiazepines and, more recently, dexmedetomidine. However, propofol causes hypotension; benzodiazepines can increase the risk of ICU-related delirium; and dexmedetomidine is not widely available due to cost. Clonidine stimulates pre-synaptic alpha-2 adrenoreceptors within the brainstem, decreasing norepinephrine release while enhancing parasympathetic activity. Robust evidence remains lacking for the use of clonidine as a sedative in the pediatric critically ill population. This systematic review and meta-analysis investigates the efficacy and safety of clonidine as a sedative in critically ill patients requiring invasive mechanical ventilation.

Methods: Authors performed a comprehensive search of MEDLINE, EMBASE, CINAHL and the Cochrane trial registry. They included 8 RCTs (n=642 patients) that compared clonidine to any non-clonidine regimen in critically ill patients, excluding neonates, requiring mechanical ventilation.

Results: Four trials enrolled children and four enrolled adults. Clonidine was administered intravenously in six trials and via the enteral route in two trials. Most trials used clonidine as an adjunctive agent added to an established sedative regimen, generally consisting of a benzodiazepine and/or an opioid. A single trial used clonidine as a stand-alone agent, compared to dexmedetomidine. With low to moderate certainty, there was no difference in the duration of mechanical ventilation, ICU mortality, hospital mortality, ICU length of stay, or hospital length of stay between the clonidine and non-clonidine groups. There was a significant reduction in the total dose of narcotics with clonidine use. Clonidine was associated with increased incidence of clinically significant hypotension, although no difference in the incidence of clinically significant bradycardia or rebound hypertension.

Conclusions / Commentary: This meta-analysis suggests that data remains insufficient to support the routine use of clonidine as a sedative in the mechanically ventilated population. Clonidine may act as a narcotic-sparing agent, albeit with an increased risk of clinically significant hypotension. Unfortunately, there was no discussion about the role of clonidine in relationships to delirium, although there was no evidence that clonidine reduced benzodiazepine usage. It remains unclear if clonidine may be “delirium reducing” similar to dexmedetomidine.

Take-away: Data remains insufficient to support the routine use of clonidine as routine sedative in the pediatric ICU. Perhaps there is a role for clonidine as an adjunctive or sedative sparing agent (e.g. by reducing opiate dosage). However, more evidence is needed to better understand the role that clonidine may play in the ICU, specifically regarding reducing or preventing delirium.

References:

1. Hayden JC, Breatnach C, Doherty DR, et al. Efficacy of α2-agonists for sedation in pediatric critical care: a systematic review. *Ped Crit Care Med* 2016;17(2):e66–75.

2. Wolf A, McKay A, Spowart C, et al. Prospective multicentre randomised, double-blind, equivalence study comparing clonidine and midazolam as intravenous sedative agents in critically ill children: the SLEEPS (Safety profiLe, Efficacy and Equivalence in Paediatric intensive care Sedation) study. *Health Technol Assess* 2014;18:1–212.

Reviewers: Rong Xiao, M.D., Ph.D., Child and Adolescent Psychiatry Fellow, University of Utah -and- Lisa Giles, M.D., University of Utah School of Medicine/Primary Children's Hospital, Salt Lake City, UT.

Source: Wang JG, Belley-Coté E, Burry L, Duffett M, Karachi T, Perri D, Alhazzani W, D'Aragon F, Wunsch H, Rochwerg B. Clonidine for sedation in the critically ill: a systematic review and meta-analysis. *Crit Care.* 2017 Feb 25; 21(1):75. Link can be found here.

Ramelteon as a Preventative Medication for Delirium?

Background and Objectives: Delirium represents an acute change in cognition due to an underlying medical condition. Up to 50% of elderly patients may develop delirium during hospitalization, and it is associated with longer length of stay, increased health system costs, and increased mortality. There are few studies examining preventative medications in high-risk populations.

Methods: Elderly patients 65 to 89 years old with no delirium on presentation, no pre-existing mood or psychotic disorder, no known cognitive fluctuation (e.g., severe liver disease), and a life expectancy greater than 48 hours were recruited from 5 hospitals in Japan. The subjects (n=67) were randomized and assigned to either 8mg/day of Ramelteon or pill placebo. The study was performed as a single (rater) blinded study; raters performed chart reviews and in-person rounds, completing Delirium Rating Scale-Revise-98 (DRS-R-98) daily with a cutoff score of 14.5.

Results: Of 1126 patients assessed for study eligibility, 1059 did not meet study criteria and only 67 were randomized to receive the pill placebo (n=34) or Ramelteon (n=33). Of those who received placebo, 11 developed delirium; however, of those who received Ramelteon only 1 developed delirium. Therefore, Ramelteon was associated with a lower risk of developing delirium (3% vs 32%; $p = 0.003$). The investigators conducted a multivariate logistic regression model to control for risk factors such as age, prior dementia, and admission diagnosis which continued to suggest patients on Ramelteon had a lower incidence of delirium ($p = 0.01$.)

Conclusion/Commentary: Ramelteon administered nightly to a high-risk population of elderly patients was associated with lower risk for the development of delirium, although this study was limited by the strict inclusion criteria and potential bias from single blinding. There is a growing body of evidence supporting the use of melatonin and melatonin receptor agonists as both a preventative medication and a treatment for delirium. It has been theorized that stress or infection may have direct effects on the pineal gland and melatonin secretion, however, the underlying neurobiological

relationship between melatonin and delirium remains unknown.

Take Away: Ramelteon and melatonin may have a role in prevention of delirium in high-risk populations. Melatonin has previously been shown to decrease risk of emergence delirium in youth undergoing anesthesia. Further data in children and adolescents is needed, ideally in larger numbers of patients in independent comparison trials between ramelteon and melatonin to determine superiority and differences, if any, of effects.

References:

1. Inouye, S.K. Delirium in older persons. N Engl J Med 2006; 354 (11): 1157-65.
2. Kain, Z.N. et. al. Preoperative Melatonin and Its Effects on Induction and Emergence in Children Undergoing Anesthesia and Surgery. Anesthesiology 2009; 111: 44-9.

Reviewer: Amy L. Meadows, MD, Kentucky Childrens Hospital/University of Kentucky College of Medicine, Lexington, KY.

Source: Hatta, K. et. al. Preventative effects of ramelteon on delirium: a randomized placebo-controlled trial. JAMA Psychiatry 2014 Apr; 71 (4): 397-403. Link here.

International Point Prevalence of Pediatric Delirium in Critically Ill Children

Background and Objectives: This article defines delirium as "acute neurologic dysfunction in the setting of serious illness." Although there is significant adult literature regarding delirium, pediatric research has been lagging due to the lack of widespread screening. Screening measures have also proven challenging, as there are several available, use varies across institutions, and each has its own limitations. The objective of this study was to estimate the point prevalence of delirium in pediatric ICU patients across multiple health care centers in various settings, as well as extrapolate innate and modifiable risk factors for the development of delirium in the critically ill pediatric population.

Methods: This was a multi-center study of 25 total institutions across the United States, Australia, New Zealand, the Netherlands, and Saudi Arabia that collected data on pediatric ICU patients on two distinct days. Fourteen institutions participated in day one, and twenty-four participated on day two. All patients in the ICUs at 8 AM on the days of the study were enrolled (994 subjects). Each patient was only rated once to gather information regarding point prevalence, not trends. The chosen screen was the Cornell Assessment of Pediatric Delirium Screen (CAPD), because it is observational, validated across all pediatric ages, and also validated in children with developmental delay. Personnel were also provided with a "developmental anchor" chart to assist with developmentally appropriate assessments. The study personnel completed the CAPD at noon on the study days, based on the observations of the nursing staff during the first four hours of their shifts (8 AM to noon). Patients were

grouped into “comatose” (heavily sedated, no response to voice), “delirious” (CAPD score of >9), “delirium/coma free,” or “unknown delirium state.” “Unknown delirium state” was used in the case of children with developmental delays with a CAPD of >9, but this was not able to be compared to their baseline functioning.

Results: Delirium state was determinable in 84% of the sample. The remaining 16% belonged to developmentally delayed children with “unknown delirium state.” This was important because 38% of the study population was developmentally delayed, and 42% of the developmentally delayed patients could not be reliably screened despite the chosen instrument's validation in that population. The overall prevalence of positive screens for delirium in the remaining 834 patients was 25% (median across institutions 23.3%). Identified demographic and illness-related risk factors for delirium included **age <2 years, mechanical ventilation, exposure to vasopressors and anti-seizure medications, and an infectious or inflammatory illness.** Potentially modifiable risk factors included: **physical restraint (odds ratio of 4 after accounting for medications and mechanical ventilation), exposure to narcotics, benzodiazepines, and steroids.** Interestingly, patients in the PICU for post-op care following general anesthesia did not seem to have the same propensity for delirium as those on similar medications during prolonged ICU treatment. **Length of ICU stay**was also a strong predictor of a positive delirium screen. Patients in the ICU for less than 6 days had a prevalence of **20%,** while patients in the ICU over 6 days had a prevalence of **38%**.

Conclusion/Commentary: The authors concluded that given the screen could be used in multiple institutions across varied cultures and practices, and determined the delirium state in 84% of the total sample, delirium screening should be universal. They predict that implementing screening will not only allow for earlier identification and management of delirium, but will also allow for a better understanding of trends in the development of delirium in pediatric patients.

Take Away: Pediatric delirium is prevalent with known poor prognostic implications but under-recognized. Implementing universal protocols is an effective bedside intervention that can lead to increased identification and treatment. There are several validated measures, but even when validated for specific populations, there are limitations and results should be interpreted with that understanding. Psychiatric Evaluation remains the Gold Standard. Avoiding narcotics and benzodiazepines whenever possible, limiting physical restraint, and transitioning out of the ICU as soon as possible are interventions that could potentially decrease the incidence of delirium.

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1. Traube C, Silver G, et al. Cornell Assessment of Pediatric Delirium: a valid, rapid, observational tool for screening delirium in the PICU. *Crit Care Med.* 2014 Mar;42(3):656-63. doi: 10.1097/CCM.0b013e3182a66b76.
2. Silver G, Kearney J, et al. Pediatric delirium: evaluating the gold standard.*Palliat Support Care.* 2015 Jun;13(3):513-6. doi: 10.1017/S1478951514000212.
3. Luetz A[1], Gensel D, et al. Validity of Different Delirium Assessment Tools for Critically Ill Children: Covariates Matter. *Crit Care Med.* 2016 Nov;44 (11):2060-2069.

Reviewer: Laura A. Markley, MD, Akron Childrens Hospital/NEOMED, Akron, OH.

Source: Traube C, Silver G, et al. Delirium in Critically Ill Children: An International Point Prevalence Study. *Crit Care Med.* 2017 Apr;45(4):584-590. doi: 10.1097/CCM.0000000000002250. Link here.

CLiPPs Feedback

We appreciate any feedback for our young, developing review series.

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