Pediatric Intensive Care Sedation: a novel model of inflammation and analgesia and sedation

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Introduction

Every year, more than 200,000 infants and children in the United States require life-saving intensive care and are treated with some form of sedation and analgesia[1,2]. It is approximated that a third survive with lasting cognitive and psychological dysfunction, collective known as pediatric post-intensive care syndrome (PICSp)[3,4]. Heralding PICSp in the intensive care unit (ICU) is delirium, that could be marker of future risk of PICSp. Pre-clinical models related to general anesthesia in healthy rodents and non-human primates have consistently identified neurotoxicity related to *N*-methyl-D-aspartate (NMDA) receptor antagonists as well as the γ-aminobutyric acid (GABA) receptor agonists and clinical models, although inconsistent, have shown a correlation between number of anesthetic exposures and future neurocognitive deficits. Interestingly enough, no preclinical models have been established to evaluate how our commonly used ICU analgesia and sedation in critically ill children impact neurotoxicity.

Hypothesis

Our aim was to establish a novel preclinical model of pediatric intensive care (PICU) sedation in the setting of critical illness through the use of *Escherichia coli* bacterial lipopolysaccharide (LPS), midazolam and morphine that produce clinically relevant behavioral effects of agitation and anxiety similar to the behavioral phenotypes often seen in the ICU.

A B

Figure 2: Whisker nuisance (WN) testing illustrating (A) normal exploratory behavior to stick nuisance and (B) anxious, agitated behavior to stick nuisance

Design/Methods

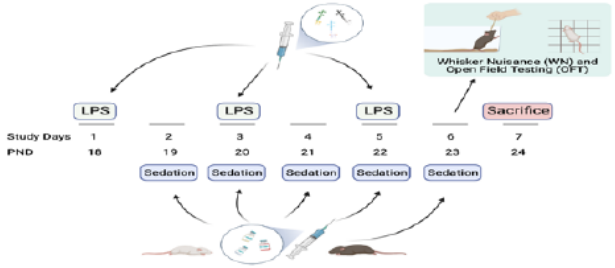

Figure 1: Illustrative study design

Male and female Long Evans and Sprague Dawley pups were divided into the following groups:

- saline (male n = 12, female n = 11)
- LPS (male n = 4, female n = 4)
- morphine + midazolam (Morph/Midaz; male n= 6, female n = 7)
- LPS + Morph/Midaz (male n = 13, female n = 11)

Pups received *E. coli* LPS or saline on study days 1 (postnatal day (PND) 18), 3 and 5 and treated with Morph/Midaz or saline twice daily on study days 2-6 (Figure 1). On study day 6 (PND 23), behavioral analysis was screened with whisker nuisance (WN) and open field testing (OFT) after animals recovered from sedation and alert with normal spontaneous activity (Figures 2 and 3)

Data was analyzed by sex and strain using Kruskal-Wallis with Dunn's posttest, with $p < 0.05$ significance. Results reported as median with interquartile range (IQR).

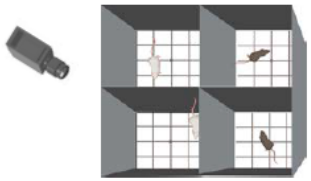

Figure 3: Open Field Testing

Results

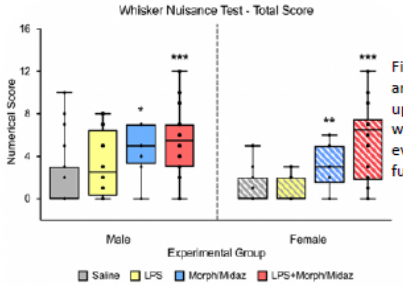

Figure 4: Whisker nuisance total score analysis by sex. Total scores based upon movement, stance, breathing, whisker position/response, stimulus evasion, grooming . See QR code for full scoring rubric.

Increased WN scores reflect agitation and anxiety behaviors. No significant OFT results

Male

Saline 0.0 [IQR 0 – 3.0] vs LPS + Morph/Midaz 5.5 [IQR 3.0 – 7.0] p = 0.0001

Saline 0.0 [IQR 0 – 3.0] vs Morph/Midaz 5.0 [IQR 3.2 – 7.0] p = 0.003

Female

Saline 0.0 [IQR 0 – 2.0] vs LPS + Morph/Midaz 6.5 [IQR 1.7 – 7.5] p = 0.0001

Saline 0.0 [IQR 0 – 2.0] vs Morph/Midaz 3.0 [IQR 1.5 – 5.0] p = 0.005

Conclusions

- A clinically relevant model of combined inflammation similar to critical illness and PICU typical sedation and analgesia is feasible
- This model produces a behavioral phenotype of anxiety/agitation often seen in our PICUs
- Further studies are warranted

Link to Contact Information, Citations and Score Sheet