Child Health Research Institute

University of Nebraska Medical Center

Children's NEBRASKA

Sedation with Midazolam in the NICU: A Double-Edged Sword

Nghi M. Nguyen[1,2,3], Adrian Flores[1,4], Jina Yi[1,2], Pranavi Athota[1], Daniel Meyer[1], Sowmya Yelamanchili[1], Gurudutt Pendyala[1,2,3,4]

[1] Department of Anesthesiology, University of Nebraska Medical Center (UNMC), Omaha, NE

[2] Department of Genetics, Cellular Biology, and Anatomy, UNMC, Omaha, NE

[3] Child Health Research Institute, Omaha, NE

[4] Department of Cellular and Integrative Physiology, UNMC, Omaha, NE

Approximately 10% of newborns in the US were born preterm (<37 weeks of gestation), facing high risks of low birth weight, respiratory issues, and heart problems due to underdevelopment. Preterm infants often undergo surgery, mechanical ventilation and are followed with prolonged periods of sedation to enhance survival chances and manage agitation. However, exposure to anesthesia/sedatives during the neonatal period has been linked to cognitive impairments, prompting FDA to issue a safety concern in 2016.

Our study focuses on midazolam (MDZ), a common neonatal sedative, for which a comprehensive understanding of its long-term impact on neurodevelopment from infancy to adulthood in clinical settings is lacking. This knowledge gap arises from recruitment challenges, consent issues, and financial constraints within the neonatal and pediatric population. To bridge this gap, our research explores the enduring effects of MDZ exposure using an ethical and appropriate preclinical rodent model. We hypothesize that prolonged early-life MDZ exposure negatively impacts neurodevelopment, leading to persistent brain function changes, including molecular and behavioral deficits, extending into adulthood. We established a dose-escalation regimen from postnatal day (P) 3 pups until P21 to mimic long-term MDZ exposure at a very early age to meticulously analyze how prolonged MDZ exposure during early development influences neurodevelopment across phenotype, molecular, and behavioral dimensions.

Our findings demonstrated that long-term MDZ exposure during the neonatal period negatively affects physical attributes in early childhood. Surprisingly, while adult bodyweights between control and MDZ-exposed rats remain comparable, the MDZ rats exhibited accelerated and robust weight gain. Notably, during adulthood, the dopamine release in MDZ-exposed rats was markedly reduced, suggesting a potential for developing binge eating behavior. We also observed elevated levels of pro-inflammatory cytokines and growth factors during adulthood, hinting at a shift in development due to early MDZ exposure. Furthermore, we observed trends of heightened anxiety-like behavior and reduced social interaction during early adolescence compared to other stages.

Collectively, our study presents a pioneering comprehensive assessment of how long-term MDZ exposure during neonatal stages impacts outcomes throughout life. These insights serve as a foundation for unraveling mechanisms that could contribute to overcoming neurodevelopmental complications associated with long-term MDZ use in neonates.