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miRNAs that regulate neurodevelopment also respond to opioid withdrawal in neonatal opioid withdrawal syndrome (NOWS) infant saliva

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Background: Current clinical decisions for the initiation of NOWS morphine therapy rely on subjective symptom scoring. Literature reports miR-146a, miR-let-7a, miR-23b, and miR-192 as microRNAs (miRNAs) that are known to regulate neurodevelopment and also respond to opioid administration in adults. **Rationale/Significance:** If such miRNA biomarkers could be identified and used to quantify withdrawal severity, risk stratification for earlier NOWS admission could be assessed and the maximum morphine dose could be predicted. **Hypothesis**: We posit that select neurodevelopmental miRNAs that have been known to respond to opioid administration in adults also respond to opioid withdrawal in neonates. **Results:** We show that miR-146a and miR-192 are significantly decreased in the saliva of 13 infants with prenatal opioid exposure compared to those of healthy infants (miR-146a, p-value= 0.0001; miR-192, p-value= 0.0003; let-7a, p= 0.093). Differences in miR-23b levels were not statistically significant, but still showed a decreased expression in NOWS patient saliva compared to healthy controls (p=0.059). When stratified by need for morphine treatment, there was a decreased expression level of miR-192 (p=0.052) in patients that required admission to the NICU for morphine therapy. Interestingly after completion of morphine therapy, miR-192 returns to levels of those in healthy infants (Welch's t-test, p=0.238), while miR-146a remains significantly decreased (student t-test, p= 0.047). **Discussion:** The identification of salivary miRNA biomarkers that can predict which NOWS patients will require morphine therapy could have several implications for management. Patients with lower levels of miR-192 (more severe withdrawal symptoms) could be admitted for NOWS morphine therapy sooner.