Model-Based Approach to Optimize Clinical Outcomes in Neonatal Opioid Withdrawal Syndrome using Real World Data

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Background

- Neonatal opioid withdrawal syndrome (NOWS) is a drug withdrawal syndrome that neonates exposed to opioids in-utero experience.
- At least 75% of the babies with NOWS need treatment with Morphine, the most commonly used drug.
- Currently, the morphine dosing adjustments are often empiric and associated with longer length of stay in the hospital (LOS).
- The aim of the study is to use an objective, real world data-driven approach to optimize morphine dosing in neonates with NOWS to improve clinical outcomes.

Methods

- Data source: Electronic medical records of a retrospective cohort of infants with NOWS (N=189) and gestational age ≥ 35 weeks admitted to the Neonatal Intensive Care Unit (NICU) at the University of Maryland Medical Center (UMMC) (2013-2017).
- Data variables: Longitudinal morphine dose and clinical response (Modified Finnegan Score (MFS)), maternal and infant baseline factors.
- Dynamic Linear Mixed Effect Model (DLME) was used to fit longitudinal MFS score with independent covariance structure.
- Covariates: Previous MFS score, Morphine Dose (mcg), Postnatal Age, Race, Methadone, Polysubstance, Benzodiazepine exposure and Clonidine use
- Model building was performed using the training data set (70% of the full data (N=121) and test data (30%, N=53) used to validate the model.

Results: Modified Finnegan Score - Morphine Dose Model

Representative observed longitudinal MFS and Morphine profile with Morphine Dose

<table>
<thead>
<tr>
<th>Year</th>
<th>Total number of infants (Number of observations)</th>
<th>Infants who received Morphine therapy</th>
<th>Type of the treatment</th>
<th>MFS (Obs)</th>
<th>MFS (Pred)</th>
<th>MFS (Obs) - MFS (Pred)</th>
<th>MFS (Obs) - MFS (Pred)</th>
<th>MFS (Obs) - MFS (Pred)</th>
<th>MFS (Obs) - MFS (Pred)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013</td>
<td>35 (7750)</td>
<td>32</td>
<td>Morphine only</td>
<td>21</td>
<td>21</td>
<td>0.0</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
<tr>
<td>2014</td>
<td>40 (9458)</td>
<td>39</td>
<td>Morphine only</td>
<td>23</td>
<td>23</td>
<td>0.0</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
<tr>
<td>2015</td>
<td>35 (8577)</td>
<td>30</td>
<td>Morphine only</td>
<td>16</td>
<td>16</td>
<td>0.0</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
<tr>
<td>2016</td>
<td>32 (214132)</td>
<td>29</td>
<td>Morphine only</td>
<td>19</td>
<td>19</td>
<td>0.0</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
<tr>
<td>2017</td>
<td>34 (47794)</td>
<td>33</td>
<td>Morphine only</td>
<td>21</td>
<td>21</td>
<td>0.0</td>
<td>-0.1</td>
<td>-0.1</td>
<td>-0.1</td>
</tr>
</tbody>
</table>

The mean absolute error was 0.55 and R² = 0.13 respectively.

- On an average, for a 100mcg increase in morphine dose, the MFS decreased by 0.5 units.
- Maternal methadone use, poly-substance drugs, race, Benzodiazepine exposure and previous morphine dose were significant predictors of MFS.
- Significant positive autocorrelations of previous two MFS with current MFS was observed ($\rho_1 = 0.55$ and $\rho_2 = 0.13$ respectively).
- The model evaluation showed that observed and predicted time on treatment is 11.0 and 9.8 days.

Model Validation – Training data: Predicted vs. Observed Mean MFS Score and Time on Morphine Treatment

- Time on Treatment – Time from first morphine dose to last morphine dose

Model Validation – Test data

- Standard deviation of prediction error (RMSE) is 1.89 and Percent mean absolute error (% MAE) is 35%

- Test data: Observed MFS vs. Predicted mean MFS for all subjects at each time intervals
- Test data : Observed MFS vs. Individual Predicted MFS

Conclusions

- A comprehensive Modified Finnegan Score – Morphine dose model controlling for maternal and infant factors was developed using the DLME framework. The model was able to describe observed data reasonably well at the population and individual level.
- The model will be further utilized to explore alternate morphine dosing protocol that can help reduce LOS and improve clinical outcomes for infant with NOWS.

References