Analgesia and Sedation Medication Use in Infants with Congenital Diaphragmatic Hernia is Associated with Adverse Outcome

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**Analgesia and Sedation Medication Use in Infants with Congenital Diaphragmatic Hernia is Associated with Adverse Outcome**

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The Children’s Hospitals Neonatal Consortium – Congenital Diaphragmatic Hernia Focus Group

**Background**

Congenital diaphragmatic hernia (CDH) occurs in 1/3000 live births and is associated with mortality in nearly 30% of affected infants.

Infants with CDH are often treated with analgesia and sedation medications despite their use being associated with negative effects on the developing brain. There is little guidance in published literature, and it is unknown how these medications are being used in the CDH population.

Better understanding of the variation in use of analgesia and sedation for these infants may allow for more targeted therapy to improve outcomes and reduce resource utilization.

**Objective**

To describe the use and variation of sedation and analgesic medications as well as short-term clinical outcomes in infants with CDH.

**Materials & Methods**

Retrospective cohort analysis (2010-16) of 19 Level IV tertiary referral NICUs participating in the Children’s Hospitals Neonatal Database (CHND).

Infants were excluded if database records were not complete, diaphragmatic repair occurred prior to referral, or death/discharge occurred at <3 days of life, or if there were surgical co-morbidities.

Medication use was captured using patient-record linkage to data in the Pediatric Health Information Systems (PHIS) dataset.

Participating centers were excluded if total number of CDH infants was ≤10 over the study period, or PHIS linkage unavailable.

Descriptive measures and variability among participating centers are reported.

Usage was stratified by use of extracorporeal membrane oxygenation (ECMO) and survival.

Primary outcomes were use, duration, and inter-center variation (CV) in analgesic and sedative medications.

Association between prolonged, concurrent use of opioids and benzodiazepines was determined by regression analysis.

**Results**

**Table 1:** Demographic data and clinical outcomes for CDH patients, stratified by survival to NICU discharge and use of ECMO.

<table>
<thead>
<tr>
<th>Variable</th>
<th>All CDH</th>
<th>Survived to Discharge</th>
<th>Non-Survivors*</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of CDH patients</td>
<td>1062</td>
<td>778</td>
<td>284</td>
<td>0.000</td>
</tr>
<tr>
<td>Median GA in weeks (IQR) at birth</td>
<td>38 (29-48)</td>
<td>38 (29-48)</td>
<td>38 (29-48)</td>
<td>0.000</td>
</tr>
<tr>
<td>Median GA in weeks (IQR) at ECMO</td>
<td>3055 (2700, 3398)</td>
<td>3125.5 (2775, 3422)</td>
<td>2824.5 (2500, 3235)</td>
<td>0.000</td>
</tr>
<tr>
<td>Gestational weeks gestation (%)</td>
<td>0.13 (0.53)</td>
<td>0.13 (0.53)</td>
<td>0.14 (0.56)</td>
<td>0.050</td>
</tr>
<tr>
<td>Admission GA</td>
<td>7.3 (2.7-4.1)</td>
<td>7.3 (2.7-4.1)</td>
<td>7.2 (2.7-4.7)</td>
<td>0.000</td>
</tr>
<tr>
<td>APACHE at 6 hrs ±</td>
<td>58.4 (45.6)</td>
<td>58.4 (45.6)</td>
<td>58.4 (45.6)</td>
<td>0.000</td>
</tr>
<tr>
<td>Left CDH (%)</td>
<td>0.45 (0.71)</td>
<td>0.45 (0.71)</td>
<td>0.45 (0.71)</td>
<td>0.000</td>
</tr>
<tr>
<td>Repair type</td>
<td>Primary</td>
<td>434 (40.2)</td>
<td>301 (85.5)</td>
<td>13 (4.4)</td>
</tr>
<tr>
<td></td>
<td>Palp</td>
<td>425 (39.7)</td>
<td>366 (107.6)</td>
<td>88 (34.3)</td>
</tr>
<tr>
<td></td>
<td>Hospital LOS (median, IQR)</td>
<td>39 (25, 73)</td>
<td>19.8 (12.9, 30.4)</td>
<td>52 (25, 98)</td>
</tr>
<tr>
<td></td>
<td>Total days of follow up</td>
<td>10.36 (2.7)</td>
<td>14.10 (2.7)</td>
<td>12.26 (2.7)</td>
</tr>
<tr>
<td></td>
<td>ECMO (%)</td>
<td>313 (29.8)</td>
<td>130 (37.8)</td>
<td>183 (30.7)</td>
</tr>
<tr>
<td></td>
<td>Days to ECMO (median, IQR)</td>
<td>11.04 (8.56-17.18)</td>
<td>8.9 (8.2, 19.9)</td>
<td>14.3 (12.28, 26.7)</td>
</tr>
<tr>
<td></td>
<td>CDH repair (%)</td>
<td>948 (89.1)</td>
<td>772 (26.9)</td>
<td>170 (10.5)</td>
</tr>
<tr>
<td></td>
<td>Cardiac catheterization (%)</td>
<td>56.5 (27.9)</td>
<td>50 (16.8)</td>
<td>150 (16.7)</td>
</tr>
<tr>
<td></td>
<td>Tracheal stenosis (%)</td>
<td>2.8 (2.2)</td>
<td>1.1 (0.64)</td>
<td>16 (3.2)</td>
</tr>
<tr>
<td></td>
<td>Gastrostomy tube placement (%)</td>
<td>442 (41.3)</td>
<td>382 (12.8)</td>
<td>100 (20.0)</td>
</tr>
<tr>
<td></td>
<td>Thoracostomy tube placement (%)</td>
<td>428 (40.3)</td>
<td>285 (83.73)</td>
<td>90 (44.59)</td>
</tr>
</tbody>
</table>

*Survivors (opioids 775/776, 99.9%, benzodiazepines 592/776, 78.3%) and non-survivors (opioids 202/202, 100%, benzodiazepines 167/202, 82.7%) received medications frequently.

**Figure 1:** Frequency of analgesia and sedation medication use among all CDH (n=1063).

**Figure 2:** Duration of opioid use and benzodiazepine use by year, 2010-2016.

**Figure 3:** Inter-center variability for duration of opioid and benzodiazepine use, capped at 60 days.

**Summary**

CDH patients treated with ECMO were:

- More frequently treated with any benzodiazepine, methadone, dexamethasone, or clonidine.
- Had longer duration of use of analgesia and sedation medications.
- Inter-center variation in use was marked, demonstrating 7-fold (opioids) and 3.5-fold (benzodiazepines) difference in duration.

36% of CDH patients had concurrent use of both opioids and benzodiazepines for at least 5 days. This was associated with:

- Longer length of hospital stay.
- Higher mortality.

**Conclusions**

Analgesia and sedation medication use is frequent with a variable pattern of utilization across centers in infants with CDH, particularly those treated with ECMO.

Though unmeasured markers of illness severity persist, concurrent use of medications appears to be associated with adverse short-term outcomes.

**Acknowledgments**

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CHNC

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