Short-term Outcomes of Infants Enrolled in Randomized Clinical Trials vs Those Eligible but Not Enrolled

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RESEARCH LETTER

Short-term Outcomes of Infants Enrolled in Randomized Clinical Trials vs Those Eligible but Not Enrolled

It is unknown whether participation in a neonatal randomized clinical trial (RCT) is independently associated with differences in outcomes. Our objective was to compare in-hospital outcomes between extremely premature infants enrolled in RCTs and those who were eligible but not enrolled in RCTs conducted by the National Institute of Child Health and Human Development Neonatal Research Network (NRN).

Methods | A retrospective analysis of infants at NRN sites between January 1, 1999, and December 31, 2012, was performed. Included infants were eligible for NRN RCTs and had outcomes recorded in the NRN very low-birth-weight registry (Generic Database [GDB]). We excluded cluster randomized trials, trials of investigational therapies (to ensure that enrolled and nonenrolled infants were likely to be treated similarly), and infants eligible for the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (a similar analysis was previously published).1

Table 1. Maternal and Infant Characteristics of Enrolled Infants in Randomized Controlled Trials and Those Eligible But Not Enrolled

<table>
<thead>
<tr>
<th>Maternal Characteristics</th>
<th>Enrolled (n = 3795)</th>
<th>Not Enrolled (n = 1594)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>No. (%)</td>
<td>Total No.</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>26.7 (6.7)</td>
<td>27.0 (6.6)</td>
<td>.09</td>
</tr>
<tr>
<td>Married</td>
<td>3773 (1677 (44)</td>
<td>1569 (773 (49)</td>
<td>.001</td>
</tr>
<tr>
<td>≥1 Prenatal visit</td>
<td>3793 (3542 (93)</td>
<td>1587 (1502 (95)</td>
<td>.08</td>
</tr>
<tr>
<td>Race</td>
<td>3792 (2053 (54)</td>
<td>1590 (822 (52)</td>
<td>.001</td>
</tr>
<tr>
<td>White</td>
<td>3792 (1624 (43)</td>
<td>1590 (674 (42)</td>
<td>.001</td>
</tr>
<tr>
<td>Black</td>
<td>3792 (115 (3)</td>
<td>1590 (94 (6)</td>
<td>.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>3691 (652 (18)</td>
<td>1501 (224 (15)</td>
<td>.02</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3785 (3014 (80)</td>
<td>1585 (1273 (80)</td>
<td>.57</td>
</tr>
<tr>
<td>Complete course</td>
<td>3772 (1604 (43)</td>
<td>1584 (710 (45)</td>
<td>.12</td>
</tr>
<tr>
<td>Infant Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>775 (145.9)</td>
<td>775 (151.5)</td>
<td>.96</td>
</tr>
<tr>
<td>Gestational age, mean (SD), wk</td>
<td>25.9 (1.9)</td>
<td>25.9 (2.0)</td>
<td>.80</td>
</tr>
<tr>
<td>Male sex</td>
<td>3795 (1908 (50)</td>
<td>1594 (778 (49)</td>
<td>.33</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>3795 (886 (23)</td>
<td>1594 (383 (24)</td>
<td>.59</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>3795 (547 (14)</td>
<td>1593 (239 (15)</td>
<td>.58</td>
</tr>
<tr>
<td>Appar score &lt;4 at 5 min</td>
<td>3534 (348 (10)</td>
<td>1483 (187 (13)</td>
<td>.001</td>
</tr>
<tr>
<td>Cardiopulmonary resuscitation at birth</td>
<td>3792 (327 (9)</td>
<td>1589 (189 (12)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* Infants were eligible but not enrolled because parent refused consent (967), consent not requested (597), and consent obtained but infant not randomized (30).

b Data are expressed as No. (%) unless otherwise indicated.

c As documented in the maternal medical record based on maternal interview. These characteristics were included because they may influence consent rates for randomized controlled trials.
extremely preterm infants who were eligible for RCTs were simultaneously enrolled in the GDB, providing a unique opportunity to assess the association between trial participation and outcomes. We included all trial participants in the enrolled group rather than just control infants because some RCTs were comparative effectiveness trials without a control group.

We did not directly compare outcomes of infants who received a specific intervention inside and outside of RCTs because exposures to some interventions, such as nitric oxide, were not consistently recorded in the GDB. One limitation is that maternal education and insurance status were not recorded consistently.

In a cohort of more than 5000 extremely preterm infants, important in-hospital outcomes were neither better nor worse in infants enrolled in RCTs compared with eligible but nonenrolled infants. These findings may reassure those who have concerns about performing RCTs in this vulnerable population.

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Author Contributions: Drs Nolen and Das had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Foglia, Nolen, DeMauro, Das, Schmidt. Acquisition, analysis, or interpretation of data: Foglia, Nolen, DeMauro, Bell, Stoll, Schmidt. Drafting of the manuscript: Foglia, Nolen. Critical revision of the manuscript for important intellectual content: Foglia, DeMauro, Das, Bell, Stoll, Schmidt. Statistical analysis: Nolen, Das. Obtained funding: Bell, Stoll. Administrative, technical, or material support: Stoll. Study supervision: Stoll, Schmidt.

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Disclaimer: This article represents the views of the authors and does not necessarily represent the views of the NICHD.

Additional Information: The entire list of the members of the NICHD Neonatal Research Network appears in Shankaran et al. 6


COMMENT & RESPONSE

Presurgery Sedation and Patient Experience

To the Editor In a randomized clinical trial by Dr Maurice-Szamburski and colleagues,1 premedication with oral lorazepam 2 hours prior to arriving in the operating room did not improve patient satisfaction after surgery and was associated with prolonged time to extubation and decreased cognitive recovery compared with placebo or no medication. These results may not indicate that all sedative premedication is unwarranted but may suggest lorazepam is inadequate.

Maurice-Szamburski and colleagues explained why lorazepam was used instead of midazolam for their trial: “The choice of lorazepam was motivated by its use in the largest survey of sedative premedication published to date,” referring to a study by Kain et al.3 There is some discrepancy between this statement and the survey results, in which among adults, the most commonly used sedative premedication was midazolam (>75%), followed by diazepam (7%), and lorazepam (2%).4 Seven years later, a follow-up survey study by Kain et al5 found that adult inpatients received midazolam most often (80%), followed by diazepam (3%), fentanyl (2%), and lorazepam (4%).

Lorazepam may have disadvantages compared with midazolam. Midazolam is a short-acting benzodiazepine with an elimination half-life of 2.0 hours to 2.5 hours, whereas lorazepam has a half-life of 10 hours to 20 hours. In a randomized clinical trial that compared midazolam with lorazepam for postoperative sedation, delays in emergence from sedation were observed in the lorazepam group.4

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To the Editor The key purpose of patient premedication with benzodiazepines is preoperative anxiolysis, which allows for safer monitoring and induction of anesthesia. In contrast, the primary outcome parameter of the study by Dr Maurice-Szamburski and colleagues was the patient’s perception quantified with a patient satisfaction index (Évaluation du Vécu de l‘Anesthésie Generale; EVAN-G) on the first postoperative day. From a clinical viewpoint, a patient’s perception on the first postoperative day is not the key parameter to judge the value of premedication.

The more important outcomes were the secondary outcomes measuring preoperative and intraoperative conditions. Anxiety upon arrival in the operating room was significantly lower (visual analog scale scores for anxiety: 35 points for lorazepam group vs 40 for placebo group). These results may not indicate that all sedative premedication is unwarranted but may suggest lorazepam is inadequate.