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

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Letters

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

We identified all eligible infants using trial screening logs. The exposure was enrollment in at least 1 RCT. Nonexposed infants were eligible for at least 1 RCT but not enrolled in any trial. The primary outcome was a composite of (1) death; (2) bronchopulmonary dysplasia (supplemental oxygen at 36 weeks postmenstrual age); (3) severe brain injury (intraventricular hemorrhage with ventricular enlargement, intraparenchymal hemorrhage, or cystic periventricular leukomalacia); or (4) severe retinopathy of prematurity (≥stage 3 or treatment in either eye).

Secondary outcomes included individual components of the primary outcome, culture-proven late-onset sepsis, and necrotizing enterocolitis (≥stage 2). Outcomes were assessed at 120 days of life, hospital discharge or transfer, or death (whichever came first).

Using SAS version 9.3 (SAS Institute Inc), we explored the association between trial enrollment and outcomes using logistic regression with and without control for prespecified baseline covariates. All tests were 2-sided with $P < .05$ indicating statistical significance. Local institutional review boards approved all RCTs and the GDB. Written informed consent was obtained for enrollment in all RCTs. Informed or waiver of consent was obtained for the GDB, as determined by local review boards.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enrolled (n = 3795)</th>
<th>Not Enrolled (n = 1594)*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>Total No. 3773</td>
<td>Total No. 1569</td>
<td>.09</td>
</tr>
<tr>
<td></td>
<td>No. (%) 26.7 (6.7)</td>
<td>No. (%) 27.0 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>1677 (44)</td>
<td>773 (49)</td>
<td>.001</td>
</tr>
<tr>
<td>≥1 Prenatal visit</td>
<td>3542 (93)</td>
<td>1502 (95)</td>
<td>.08</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>2053 (54)</td>
<td>822 (52)</td>
<td>.&lt;.001</td>
</tr>
<tr>
<td>Black</td>
<td>1624 (43)</td>
<td>674 (42)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>115 (3)</td>
<td>94 (6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>652 (18)</td>
<td>224 (15)</td>
<td>.02</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>3014 (80)</td>
<td>1273 (80)</td>
<td>.57</td>
</tr>
<tr>
<td>Complete course</td>
<td>1604 (43)</td>
<td>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</td>
<td>1908 (50)</td>
<td>.33</td>
</tr>
<tr>
<td>Multiple gestation</td>
<td>3795</td>
<td>886 (23)</td>
<td>.59</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td>3795</td>
<td>547 (14)</td>
<td>.58</td>
</tr>
<tr>
<td>Appar score &lt;4 at 5 min</td>
<td>3534</td>
<td>1483 (13)</td>
<td>.003</td>
</tr>
<tr>
<td>Cardiopulmonary resuscitation</td>
<td>3792</td>
<td>189 (12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Outborn</td>
<td>3795</td>
<td>209 (13)</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.
The primary outcome did not differ significantly between groups (68% in enrolled group vs 69% in eligible but not enrolled group; adjusted odds ratio, 1.08 [95% CI, 0.93-1.26]; \( P = .29 \)). There were no differences in the secondary outcomes in the adjusted analysis (Table 2). Furthermore, the primary outcome did not differ between groups when analyzed by individual trial.

**Discussion** | Only a few studies with divergent findings have examined whether trial participation is associated with differences in outcomes in preterm newborns.\(^4,5\) The present study did not find differences in mortality or neonatal morbidity between trial participants and nonparticipants. Similarly, meta-analyses of studies of adults and older children have demonstrated no significant differences in outcomes between trial participants and nonparticipants who were treated similarly outside trials.\(^4,5\)

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.

### Table 2. Primary and Secondary Outcomes by Enrollment Status and Primary Outcome by Individual Trial

| Primary Outcome by Individual Trial | Total No. | No. (%) | Total No. | No. (%) | Unadjusted OR (95% CI) | P Value | Adjusted OR (95% CI) | P Value
<table>
<thead>
<tr>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome(^a)</td>
<td>3717</td>
<td>2545 (68)</td>
<td>1555</td>
<td>1076 (69)</td>
<td>0.97 (0.85-1.10)</td>
<td>.60</td>
<td>1.08 (0.93-1.26)</td>
<td>.29</td>
</tr>
</tbody>
</table>

### Secondary Outcomes

| Secondary Outcomes | Total No. | No. (%) | Total No. | No. (%) | Unadjusted OR (95% CI) | P Value | Adjusted OR (95% CI) | P Value
<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>3793</td>
<td>823 (22)</td>
<td>1594</td>
<td>361 (23)</td>
<td>0.95 (0.82-1.09)</td>
<td>.44</td>
<td>1.01 (0.86-1.19)</td>
<td>.88</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>3087</td>
<td>1522 (49)</td>
<td>1284</td>
<td>646 (50)</td>
<td>0.96 (0.84-1.09)</td>
<td>.54</td>
<td>1.08 (0.93-1.25)</td>
<td>.32</td>
</tr>
<tr>
<td>Severe brain injury</td>
<td>3670</td>
<td>719 (20)</td>
<td>1505</td>
<td>279 (19)</td>
<td>1.07 (0.92-1.25)</td>
<td>.38</td>
<td>1.10 (0.93-1.30)</td>
<td>.27</td>
</tr>
<tr>
<td>Severe retinopathy of prematurity</td>
<td>3030</td>
<td>675 (22)</td>
<td>1256</td>
<td>290 (23)</td>
<td>0.95 (0.82-1.12)</td>
<td>.56</td>
<td>0.99 (0.83-1.18)</td>
<td>.88</td>
</tr>
<tr>
<td>Late-onset sepsis</td>
<td>3641</td>
<td>1466 (40)</td>
<td>1520</td>
<td>566 (37)</td>
<td>1.14 (1.00-1.29)</td>
<td>.04</td>
<td>1.09 (0.95-1.24)</td>
<td>.22</td>
</tr>
<tr>
<td>Necrotizing enterocolitis</td>
<td>3778</td>
<td>394 (10)</td>
<td>1577</td>
<td>175 (11)</td>
<td>0.93 (0.77-1.13)</td>
<td>.47</td>
<td>0.94 (0.77-1.14)</td>
<td>.53</td>
</tr>
</tbody>
</table>

Abbreviations: CPAP, continuous positive airway pressure; OR, odds ratio.\(^6\)

\(^a\) Indicates those who were eligible but not enrolled. See footnote “a” in Table 1 for reasons.

\(^b\) Adjusted in logistic regression for gestational age, antenatal steroids, race, sex, multiple gestation, small for gestational age, cardiopulmonary resuscitation at birth, outborn status, and treatment center.

\(^c\) Composite of 1 or more of the following: death; bronchopulmonary dysplasia; severe brain injury; or retinopathy of prematurity at 120 days of life, discharge, transfer, or death.

\(^d\) Unadjusted \( P \) value calculated using the Fisher exact test and exact 95% CIs calculated for the ORs presented to account for small sample sizes in some studies.
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.

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

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Independent Statistical Analysis: Data collected at participating sites of the NICHD Neonatal Research Network were transmitted to RTI International, the data coordinating center for the network, which performed the storage, management, analysis, and interpretation of the data.

Group Information: Members of the NICHD Neonatal Research Network who contributed to this article: Rosemary D. Higgins, MD (NICHD, Bethesda, Maryland), Brenda B. Poindexter, MD, MS (Department of Pediatrics, Indiana University School of Medicine, Indianapolis), Seetha Shankaran, MD (Department of Pediatrics, Wayne State University, Detroit, Michigan), and Krisa P. Van Meurs, MD (Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Palo Alto, California).

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

3. Rüegger CM, Kraus A, Koller B, et al. Randomized controlled trials in very preterm infants: does inclusion in the lorazepam group.4
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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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.


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 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. 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 (79%), and lorazepam (2%). Seven years later, a follow-up survey study by Kain et al. 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

To the Editor

Presurgery Sedation and Patient Experience

To the Editor In a randomized clinical trial by Dr Maurice-Szamburski and colleagues, premedication with oral lorazepam 2 hours prior to arriving in the operating room did not improve patient satisfaction after surgery and was associated with no statistically significant differences between lorazepam and midazolam in terms of patient satisfaction index, emergence time, or time to endotracheal extubation.

In conclusion, lorazepam appears to be a suitable premedication for pediatric patients undergoing surgery, offering improved patient satisfaction and reduced anxiety compared to midazolam.