Neurodevelopmental Outcomes of Very Low-Birth-Weight Infants With Necrotizing Enterocolitis

A Systematic Review of Observational Studies

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Objective: To systematically review observational studies reporting long-term neurodevelopmental outcomes in very low-birth-weight neonates surviving after necrotizing enterocolitis (NEC).

Data Sources: The Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, CINAHL (Cumulative Index to Nursing and Allied Health), and proceedings of the Pediatric Academic Societies (published in Pediatric Research since 1970) were searched in June and September 2006. The reference lists of identified studies and personal files were searched.

Study Selection: All studies with a control group were eligible for inclusion.

Main Outcome Exposure: Necrotizing enterocolitis (stage II or higher) vs no NEC.

Main Outcome Measure: Neurodevelopmental impairment at 1 year or older of corrected age.

Results: Eleven nonrandomized studies, including 5 with “matched controls,” were included in the analyses. The risk of long-term neurodevelopmental impairment was significantly higher in the presence of at least stage II NEC vs no NEC (odds ratio, 1.82; 95% confidence interval, 1.46-2.27). Significant heterogeneity (I²=47.9%; P=.06) between the studies indicated variations in patient, illness, and intervention characteristics and in follow-up methods. Patients with NEC requiring surgery were at higher risk for neurodevelopmental impairment vs those managed medically (odds ratio, 1.99; 95% confidence interval, 1.26-3.14). Results of analyses based on study design, follow-up rate, and year of birth were not statistically significantly different from those of the overall analysis. Risk of cerebral palsy and cognitive and severe visual impairment was significantly higher in neonates with NEC.

Conclusion: Survivors of stage II or higher NEC are at risk for long-term neurodevelopmental impairment, especially if they require surgery for the illness.

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Necrotizing enterocolitis (NEC) is the most common neonatal gastrointestinal emergency. It is mainly associated with prematurity, with full-term neonates accounting for only 5% to 25% of all cases. The incidence of this potentially fatal illness is reported to be 5% to 10% in very low-birth-weight (VLBW) neonates. Extremely low-birth-weight (ELBW) neonates (birth weight <1000 g) with gestation less than 28 weeks are most susceptible. The mortality (20%-40%) and morbidity rates after a diagnosis of definite NEC continue to be high, especially in ELBW neonates. Preterm and VLBW neonates with NEC may be at high risk for long-term neurodevelopmental impairment (NDI) given the role of inflammatory cytokines in the illness and associated comorbidities, such as sepsis and nutritional deprivation. Survivors of surgically managed NEC may especially be at a higher risk after exposure to higher levels of pro-inflammatory cytokines for a longer duration. Several observational studies have reported long-term NDI in NEC survivors. Generalization of the studies’ individual results is difficult owing to variations in study design, patient population, severity of illness, type of surgical intervention, method of follow-up, age at follow-up, and possibly the standard of neonatal intensive care and clinical practices at the time. However, this variability provides a unique opportunity to pool these data and evaluate the generalizability of the results. A systematic review and meta-analysis was undertaken to...
assess whether (1) NEC is associated with an increased risk of long-term NDI and (2) the risk of such an impairment is even higher in surgically compared with medically managed NEC in preterm VLBW neonates.

METHODS

The standard search strategy of the Cochrane Neonatal Review Group was followed. The Cochrane Central Register of Controlled Trials (The Cochrane Library, Issue 3, 2006), MEDLINE (using the PubMed interface offered by the US National Library of Medicine), EMBASE (Excerpta Medica), CINAHL (Cumulative Index to Nursing and Allied Health), and proceedings of the Pediatric Academic Societies (published in Pediatric Research since 1970) were searched in June and September 2006. The reference lists of identified studies and personal files (proceedings of the European Society for Pediatric Research and Pediatric Gastroenterology conferences) were searched. All study designs with a control group were eligible for inclusion in the review. No language restriction was applied. The following PubMed search strategy was used: (neonate or infant, newborn [Medical Subject Headings (MeSH)]) and (necrotizing enterocolitis or necrotising enterocolitis or enterocolitis, necrotizing [MeSH]) and (mental retardation [MeSH] or cerebral palsy [MeSH] or psychomotor disorders [MeSH] or cerebral palsy [MeSH] or blindness [MeSH] or deafness [MeSH] or impair or long-term or outcome or neurodevelopment). The following preselected criteria justified inclusion of any study in the analysis:

1. Studies involving VLBW infants, that is, gestational age less than 32 complete weeks or birth weight less than 1500 g.
2. Use of modified Bell staging for defining stages of NEC.14,15
3. Only studies reporting on stage II or higher NEC were eligible for inclusion.
4. Long-term follow-up at 1 year or older using a validated method for neurodevelopmental assessment, such as the Bayley or Griffiths’ scale.
5. The presence of an a priori definition of moderate to severe NDI that included 1 or more of the following: scores less than 2 SDs of normal on the Bayley or Griffiths scale of assessment, cerebral palsy (CP), severe visual impairment, and severe hearing impairment. Clear definitions of CP, severe visual impairment, and severe hearing impairment were required.

All of us searched the literature independently and assessed the inclusion criteria and quality of the trials (including completeness of follow-up and blinding of outcome assessors). Two of us (S.M.S. and G.C.D.) independently extracted the data. Inconsistencies were resolved by discussion. Data extraction, statistical calculations, and graphing of results of meta-analyses were performed using a software program (Review Manager version 4.2.8; The Cochrane Collaboration, Oxford, England). Odds ratios (ORs) (“matched-control” studies and pooling of all included studies) and relative risks (RRs) (subgroup analysis of cohort studies) with 95% confidence intervals (CIs) were calculated. A statistical model assuming the same heterogeneity among studies (random effects) was used for summarizing effects. Heterogeneity was estimated by means of the I² statistic.18

The following sensitivity and subgroup analyses were preplanned:

1. Pooling of data from all studies (NEC vs no NEC, surgically managed NEC vs no NEC, and medically managed NEC vs no NEC) and separately for cohort studies and those with a matched-control design (NEC vs no NEC).

2. Exclusion of studies with less than 80% follow-up given that follow-up is critical in correct interpretation of long-term neurodevelopmental outcomes.
3. Exclusion of studies involving neonates born in the pre-surfactant era given that survival and long-term outcome of high-risk neonates has improved dramatically since the availability of surfactant in the 1990s.
4. Comparison of surgically vs medically managed NEC.
5. Comparison of the Bayley mental (MDI) and psychomotor (PDI) developmental indices was planned because psychomotor rather than cognitive impairment has been reported as a significant issue in survivors of NEC.19

The guidelines for reporting of the Meta-analysis Of Observational Studies in Epidemiology Group were followed where appropriate.20

RESULTS

We identified 695 abstracts using the prespecified search strategy. Eighteen studies5,6,10-13,19,21-31 (7 matched-control and 11 cohort studies) reporting long-term NDI outcomes in preterm VLBW neonates with stage II or higher NEC were retrieved for detailed evaluation. Seven studies reported as “case-control” studies used gestation- or birth weight–matched controls for each case of NEC, with NDI as the outcome of interest. However, in a true case-control study, the cases would be children with NEC, the controls would be children without NEC, and the exposure of interest would be NEC. We, therefore, labeled these 7 retrospective comparative studies as matched-control studies for the purpose of this review. They are, however, analyzed separately because they used matched controls, and data on the entire control cohort were not available. No interventional studies reporting long-term NDI were found.

The characteristics of 11 studies (5 matched-control5,11,13,21,27 and 6 cohort5,10,12,22,24,30,31 studies) involving 6480 VLBW survivors of NEC included in the analysis are summarized in Table 1 and Table 2. The characteristics of 7 studies5,10,21,23,28,30 excluded from the analysis and the reasons for their exclusion are summarized in Table 3.

ANALYSIS COMBINING ALL STUDIES (NEC VS NO NEC)

More neonates with stage II or higher NEC had long-term NDI compared with those without NEC (183/427 [42.9%] vs 1267/3812 [33.2%]). Meta-analysis of data from 8 studies (N = 4239) using a fixed-effects model estimated a significant risk of long-term NDI in the presence of stage II or higher NEC compared with those without NEC (OR, 1.82; 95% CI, 1.46-2.27) (Figure 1). There was significant heterogeneity between the studies (I² = 47.9%; P = .06), indicating variations related to several factors, including patient, illness, and surgical intervention characteristics and long-term follow-up methods, as mentioned previously. Use of a random-effects model did not indicate any significant difference in the results (NEC vs no NEC: OR, 2.37; 95% CI, 1.51-3.71). The median (range) survival rate using the available data was 56/79 (70.9%) (40/84-75/86 [47.6%-87.2%]) for the NEC group and 3556/4588 (77.5%) (766/1422-560/703 [53.9%-79.7%]) for the no NEC group.
SURGICAL VS MEDICAL MANAGEMENT

Meta-analysis of data from 3 studies6,10,12 (N = 3495) showed a significant risk of NDI when comparing surgically managed NEC with no NEC (OR, 2.00; 95% CI, 1.43-2.79). There was no significant risk of NDI when comparing medically managed NEC with no NEC (N = 3498) (OR, 1.08; 95% CI, 0.76-1.54). Use of a random-effects model did not show any significant difference in the results (surgically managed NEC vs no NEC: OR, 2.0; 95% CI, 1.43-2.79; medically managed NEC vs no NEC: OR, 1.09; 95% CI, 0.77-1.55). Subgroup analysis assessing the risk of NDI by method of NEC management estimated a pooled OR of 1.99 (95% CI, 1.26-3.14) for patients requiring surgery compared with those managed medically (Figure 2).

SENSITIVITY ANALYSES

Results of the different sensitivity analyses based on the study design, follow-up rate, and year of birth were not significantly different from those of the combined analysis of NEC vs no NEC: (1) matched-control studies (OR, 3.09; 95% CI, 1.76-5.41) or cohort studies (RR, 1.33; 95% CI, 1.17-1.51); and OR, 1.64; 95% CI, 1.29-2.09); (2) studies with follow-up rates of 80% or greater (OR, 2.60; 95% CI, 1.67-4.05); and (3) studies involving only neonates born in 1990 or later (OR, 1.79; 95% CI, 1.40-2.29).

ANALYSIS OF COMPONENTS OF NDI

Analysis of individual components of NDI showed a significantly increased risk of CP and cognitive and severe visual impairment but not of severe hearing impairment in neonates with NEC (Table 4). Assessment of mean Bayley PDI and MDI scores was possible only for the comparison of surgically vs medically managed NEC owing to lack of data. In this analysis, pooled data from 2 studies10,26 incorporating 248 neonates showed a significant reduction in mean PDI scores (weighted mean difference, −6.56; 95% CI, −10.82 to −2.30) but not MDI scores (weighted mean difference, −2.69; 95% CI, −6.14 to 0.75) in those with surgically vs medically managed NEC.

COMMENT

These results indicate that the diagnosis of stage II or higher NEC is associated with an increased risk of long-term NDI in preterm VLBW neonates. The risk is even higher in the presence of surgically managed (usually stage III) NEC. Caution is necessary in interpretation of these results given the variability in the study, patient, and illness characteristics mentioned previously. The fact that the results are based on matched-control and cohort studies rather than on randomized controlled trials is important. Pooling of data from matched-control studies requires the use of ORs rather than RRs for effect estimation, which can lead to overestimation of the effect size, particularly if the baseline risk is high.32 However, all significant ORs calculated in this meta-analysis are less than 2.8, and calculation of RRs instead of ORs for cohort studies did not change the results significantly.

This systematic review included the large National Institute of Child Health and Human Development study by Hintz et al,33 with a follow-up rate of 77% in the NEC group. Although this study received a weight of 75% in the overall analyses, its exclusion in a sensitivity analysis owing to lack of data. In this analysis, pooled data from 2 studies10,26 incorporating 248 neonates showed a significant reduction in mean PDI scores (weighted mean difference, −6.56; 95% CI, −10.82 to −2.30) but not MDI scores (weighted mean difference, −2.69; 95% CI, −6.14 to 0.75) in those with surgically vs medically managed NEC.
out changing the results significantly. The differences in the definition of NDI are an important issue. In the most recent studies, neonates with mild to moderate CP were classified as having moderate to severe impairment, whereas other studies regarded only nonambulatory CP as a component of moderate to severe impairment. Most studies defined cognitive and psychomotor impairment as a score greater than 2 SDs below the mean of a validated scale of neurodevelopmental assessment. However, Walsh et al used a cutoff point of a Bayley score less than 80. The definition of moderate to severe impairment based on mild to moderate CP and Bayley scores less than 80 can overestimate the impairment rates. Holmsgaard and Petersen did not use a standardized score for overall assessment of NDI, but the description of impairment indicates it to be severe. In any case, their study is not significant in terms of the present overall results given that it contributes only 1 case with NDI.

The role of a range of confounding factors, including prematurity, intrauterine growth restriction, sepsis, postnatal growth restriction, and exposure to glucocorticoids, as well as hyperbilirubinemia, apnea, preterm rupture of membranes, and chorioamnionitis, also must not be forgotten in such high-risk, especially ELBW, neo-

### Table 2. Methods of Assessment and Definitions of NDI

<table>
<thead>
<tr>
<th>Study</th>
<th>Scale</th>
<th>Definitions</th>
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<tbody>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hinz et al, 2005</td>
<td>BSID 2</td>
<td>NDI: ≥1 of the following: MDI &lt;70, PDI &lt;70, CP, blindness, deafness.</td>
</tr>
<tr>
<td>Castro et al, 2004</td>
<td>BSID 2</td>
<td>CP: Nonprogressive central nervous system disorder characterized by abnormal muscle tone in ≥1 extremity and abnormal control of movement and posture.</td>
</tr>
<tr>
<td>Holmsgaard and Petersen, 1996</td>
<td>Undefined (clinical assessment)</td>
<td>NDI: ≥1 of the following: severe mental retardation or autism, severe CP (unable to walk), blindness, deafness.</td>
</tr>
<tr>
<td>Waugh et al, 1996</td>
<td>Griffiths and McCarthy Index</td>
<td>CP: Severe, unable to function independently even with assistance; moderate, impaired but able to function independently with assistance; mild, minimal or no functional impairment.</td>
</tr>
<tr>
<td>Simon et al, 1993</td>
<td>BSID 1</td>
<td>CP: Nonprogressive motor impairment characterized by abnormal muscle tone in ≥1 extremity and decreased range or control of movements.</td>
</tr>
<tr>
<td>Walsh et al, 1989</td>
<td>BSID 1 and Stanford-Binet</td>
<td>NDI: GO &lt;76 (&lt;2 SDs below mean).</td>
</tr>
<tr>
<td>Matched-control*</td>
<td>Soraisham et al, 2006</td>
<td>NDI: ≥1 of the following: cognitive delay (MDI or IQ &lt;2 SDs below mean), CP, visual impairment, deafness.</td>
</tr>
<tr>
<td>Yeh et al, 2004</td>
<td>BSID 2</td>
<td>CP: Severe, nonambulatory; moderate or severe CP, blindness, deafness.</td>
</tr>
<tr>
<td>Sonntag et al, 2000</td>
<td>Griffiths</td>
<td>CP: Moderate to severe, walking aids needed/child unlikely ever to walk; mild, ambulatory, motor impairment interfering only slightly with daily activities.</td>
</tr>
<tr>
<td>Tobiansky et al, 1995</td>
<td>Griffiths and Stanford-Binet</td>
<td>NDI: ≥1 of the following: severe mental retardation or autism, severe CP, blindness, deafness.</td>
</tr>
</tbody>
</table>

| Abbreviations: BSID, Bayley Scales of Infant Development; CP cerebral palsy; GQ, Griffiths quotient; MDI, mental developmental index; NDI, neurodevelopmental impairment; PDI, psychomotor developmental index. |
| *Retrospective comparative studies. |
nates.39,33-42 Mere pooling of data on neurodevelopmental outcomes does not assess the impact of these confounding factors. The frequently observed interplay among prematurity, intrauterine growth restriction, sepsis, NEC, and postnatal growth restriction due to nutrient deprivation is especially important when evaluating long-term NDI in extremely preterm neonates.

Interpretation of these results is difficult because they relate to follow-up at a younger age, which may not reflect the true “long-term” outcomes.26 Simon et al26 re-

Table 3. Characteristics of the 7 Excluded Studies

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>NEC, No./Total No.</th>
<th>No NEC, No./Total No.</th>
<th>OR (95% CI)</th>
<th>Weight, %</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 Cohort Studies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hintz et al,10 2005</td>
<td>119/234</td>
<td>1014/2531</td>
<td>75.27</td>
<td>1.55 (1.18-2.02)</td>
<td></td>
</tr>
<tr>
<td>Holmsgaard and Petersen,24 1996</td>
<td>1/4</td>
<td>31/134</td>
<td>1.20</td>
<td>1.11 (0.11-11.03)</td>
<td></td>
</tr>
<tr>
<td>Waugh et al,21 1996</td>
<td>7/23</td>
<td>13/171</td>
<td>1.91</td>
<td>5.32 (1.86-15.24)</td>
<td></td>
</tr>
<tr>
<td>Walsh et al,12 1989</td>
<td>12/36</td>
<td>173/768</td>
<td>9.24</td>
<td>1.71 (0.84-3.50)</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>297</td>
<td>3602</td>
<td>87.63</td>
<td>1.64 (1.29-2.09)</td>
<td></td>
</tr>
</tbody>
</table>

| **02 Matched-Control Studies** |                    |                       |             |           |             |
| Soraisam et al,11 2006 | 11/46              | 10/100                | 4.28       | 2.83 (1.10-7.25) |
| Yeh et al,13 2004      | 13/15              | 11/30                 | 0.87       | 11.23 (2.13-59.26) |
| Sonntag et al,27 2000  | 11/20              | 9/40                  | 2.41       | 4.21 (1.33-13.32) |
| Tobiansky et al,6 1995 | 9/49               | 6/40                  | 4.81       | 1.28 (0.41-3.95) |
| **Subtotal**           | 130                | 210                   | 12.37      | 3.09 (1.76-5.41) |

| **Total Events** | 427                | 3812                  | 100.00     | 1.82 (1.46-2.27) |

Figure 1. Meta-analysis of neurodevelopmental impairment data from 8 studies using a fixed-effects model: necrotizing enterocolitis (NEC) vs no NEC. Plot displays odds ratios (ORs) for all included studies and separately for cohort and matched-control studies. CI indicates confidence interval; VLBW, very low-birth-weight. Squares represent the point estimate of treatment effect of each study, with a horizontal line extending on either side of the square representing the 95% CI. Arrowheads indicate a wide CI that is compressed to fit the scale. Solid diamonds represent the overall and subgroup OR estimate of the studies presented in the meta-analysis. The widths of the diamonds represent the 95% CI of the OR. The midline of the forest plot, corresponding to an OR of 1, represents a no-effect line.
reported a higher incidence of motor delays at 8 and 15 months of corrected age in VLBW neonates requiring surgery for NEC. The motor delays, however, had resolved by 24 months in 5 of the 6 cases, highlighting the importance of longer follow-up. Last, the impact of reporting bias and changes (known/unknown) in clinical practice across time also cannot be denied. Castro et al investigated possible bias in neurodevelopmental and somatic growth assessment at 18 to 22 months’ postmenstrual age among 1483 ELBW survivors (born in 1993-1994) from many centers. Compared with children who were lost to follow-up, those who were compliant with follow-up were more likely to have been 1 of a multiple birth, to have received postnatal glucocorticoids, and to have had chronic lung disease. Chronic lung disease was associated with increased risk of CP. Scores less than 70 on the MDI and PDI were found in 37% and 29% of children evaluated at follow-up, respectively. Prediction models revealed that 34% and 26% of those in the no-visit group would have had MDI and PDI scores less than 70, respectively. Compliant children tended to have a greater incidence of MDI scores less than 70 compared with those predicted in the no-visit group but not of PDI scores less than 70. Cerebral palsy was identified in 17% of the compliant group and was predicted for 18% of the no-visit group. Predicted probabilities of having CP were marginally higher in no-visit infants compared with those who were compliant with follow-up. Overall, the results indicate that follow-up results based on those who are compliant with follow-up might be an overestimation of adverse outcomes in ELBW survivors. Despite all the issues discussed herein, the consistency of the association between NEC and NDI across all studies and sensitivity analyses and the biological plausibility of cerebral white matter injury from proinflammatory cytokines (implicated in the pathogenesis of NEC), however, support the present results. 

The finding that an increased risk of NDI is even more relevant to neonates with surgically managed NEC probably reflects the severity of illness with resultant exposure to a higher level of proinflammatory cytokines for a longer duration and the fact that surgical intervention itself is associated with proinflammatory cytokine surge and NDI. Survivors of surgical NEC are also expected to be subjected to longer and possibly more significant exposure to suboptimal nutrition and multiple episodes of sepsis due to prolonged enteral feed intolerance and exposure to suboptimal nutrition and multiple episodes of sepsis.
nutrition, and, in some cases, short bowel syndrome. Note that bias may have been introduced by separating patients into groups based on the need for surgery. However, analysis by an objective criterion, such as the presence or absence of bowel perforation, could not be performed because of lack of specific data.

The clinical relevance of the present results needs to be discussed. Because the diagnosis of definite NEC is associated with long-term NDI and the risk is even higher with surgically managed NEC, prevention, early diagnosis, optimal treatment, and long-term follow-up after the illness is important. Experts have already pointed out the need to emphasize the importance and significance of the “risky business” of long-term follow-up while counseling the parents of neonatal survivors of NEC. Given the poorly understood and multifactorial pathogenesis of the illness and the fact that prematurity is the single most important risk factor, primary prevention of NEC is expected to be difficult. Early diagnosis and prevention of progression of stage II NEC to perforation and peritonitis (stage III) are, thus, equally important. Advances in laparoscopic techniques for the tiny patients are expected to be helpful in early diagnosis. The results of recent experimental studies indicate the potential role of immunomodulators in secondary prevention of the illness. Current evidence indicates that the early outcomes in preterm neonates with perforated NEC are not significantly different using either peritoneal drains or laparotomy. Long-term follow-up results of such studies are important because the less invasive nature of peritoneal drains and laparotomy may be associated with less NDI.

Just at the time of reporting these results, Rees et al also reported their meta-analysis on neurodevelopmental outcomes of preterm neonates with medically and surgically managed NEC with almost identical results. The differences in methods, however, need to be pointed out. Rees et al did not address the critical issue of variations in the definition of NDI in the studies. Sensitivity analyses (analyzing cohort and matched-control studies separately, assessing cohort studies by means of ORs and RRs, and excluding studies from the presurfactant era and studies with follow-up rates <80%) are lacking. These data also include the most recent study by Soraisham et al evaluating the impact of NEC on the neurodevelopmental and growth outcomes in preterm neonates with birth weight of 1250 g or less.

In summary, these results indicate that survivors of stage II or higher NEC are at high risk for NDI. The risk is even higher in survivors of NEC who require surgical intervention. The need for continued long-term follow-up and counseling of the parents about its importance is emphasized. Continued research toward primary and secondary prevention of NEC is critical in avoiding or at least minimizing NDI associated with the illness.

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Author Contributions: All the authors had full access to all the data in the systematic review and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Patole. Acquisition of data: Schulzke, Deshpande, and Patole. Analysis and interpretation of data: Schulzke, Deshpande, and Patole. Drafting of the manuscript: Schulzke and Patole. Critical revision of the manuscript for important intellectual content: Schulzke, Deshpande, and Patole. Statistical analysis: Schulzke, Deshpande, and Patole. Administrative, technical, and material support: Schulzke. Study supervision: Patole.

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REFERENCES