Interventions To Prevent Retinopathy of Prematurity: A Meta-analysis
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abstract

CONTEXT: The effectiveness of many interventions aimed at reducing the risk of retinopathy has not been well established.

OBJECTIVE: To estimate the effectiveness of nutritional interventions, oxygen saturation targeting, blood transfusion management, and infection prevention on the incidence of retinopathy of prematurity (ROP).

DATA SOURCES: A comprehensive search of several databases was conducted, including Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and Scopus through March 2014.

STUDY SELECTION: We included studies that evaluated nutritional interventions, management of supplemental oxygen, blood transfusions, or infection reduction and reported the incidence of ROP and mortality in neonates born at <32 weeks.

DATA EXTRACTION: We extracted patient characteristics, interventions, and risk of bias indicators. Outcomes of interest were any stage ROP, severe ROP or ROP requiring treatment, and mortality.

RESULTS: We identified 67 studies enrolling 21,819 infants. Lower oxygen saturation targets reduced the risk of developing any stage ROP (relative risk [RR] 0.86, 95% confidence interval [CI], 0.77–0.97) and severe ROP or ROP requiring intervention (RR 0.58, 95% CI, 0.45–0.74) but increased mortality (RR 1.15, 95% CI, 1.04–1.29). Aggressive parenteral nutrition reduced the risk of any stage ROP but not severe ROP. Supplementation of vitamin A, E, or inositol and breast milk feeding were beneficial but only in observational studies. Use of transfusion guidelines, erythropoietin, and antifungal agents were not beneficial.

LIMITATIONS: Results of observational studies were not replicated in randomized trials. Interventions were heterogeneous across studies.

CONCLUSIONS: At the present time, there are no safe interventions supported with high quality evidence to prevent severe ROP.
Retinopathy of prematurity (ROP) is a disorder of the developing retina in preterm infants and is a leading cause of childhood blindness.\textsuperscript{1} ROP primarily affects neonates born at <32 weeks gestational age, with the risk and severity of ROP increasing with decreasing gestational age. Depending on the population studied, 20% to 50% of very low birth weight (VLBW, birth weight <1500 g) infants will develop ROP, with 4% to 19% having severe ROP (stages 3–5).\textsuperscript{2,3} 

Although incompletely understood, the pathogenesis of ROP involves multiple signaling factors and has been characterized by 2 phases.\textsuperscript{3} The first phase begins after preterm birth and involves growth cessation of the retinal vasculature. Then at ~32 weeks postmenstrual age, retinal neovascularization begins, marking the initiation of phase 2. Although preterm delivery is the primary risk factor for the development of ROP, multiple other modifiable clinical factors have been associated with an increased risk of ROP. These correlate well with the current understanding of ROP pathogenesis and include poor postnatal weight gain in the first 6 weeks of life,\textsuperscript{4,5} hyperoxia,\textsuperscript{6–8} exposure to packed red blood cell (PRBC) transfusions,\textsuperscript{9,10} and late onset sepsis.\textsuperscript{11–13} 

The objective of this meta-analysis was to study the effect and magnitude of the benefit of multiple interventions aimed at the prevention of ROP in preterm neonates <32 weeks gestational age. Four categories of interventions were selected based on the current understanding of ROP pathophysiology and included: (1) postnatal nutrition, (2) management of supplemental oxygen, (3) PRBC transfusions, and (4) infection reduction.

METHODS

Evidence Acquisition

This systematic review is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.\textsuperscript{14} 

Data Sources and Search Strategy

A comprehensive search of several databases was conducted from each database’s earliest inception to March 2014, any language, in infants. The databases included Ovid Medline In-Process & Other Non-Indexed Citations, Ovid Medline, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study’s principal investigator. Controlled vocabulary supplemented with keywords was used to search for comparative studies of interventions for the prevention of ROP. The actual strategy is available in the Supplemental Information. To identify additional candidate studies, we reviewed reference lists from eligible studies.

Selection of Studies

Initial screening of the identified studies was performed by 4 independent reviewers working in duplicates based on the titles and abstracts, taking into consideration the inclusion criteria. After removing irrelevant and non-original studies, full-text screening was then performed to assess eligibility for final inclusion. Discrepancies were resolved through discussion and consensus.

We used a list of inclusion criteria set a priori for the initial and full article screening. We sought studies that included preterm infants <32 weeks gestational age who were cared for in a NICU. Interventions of interest comprised 4 main categories including postnatal nutritional interventions, management of supplemental oxygen, PRBC transfusions, and interventions aimed at reducing infections. Main outcomes of interest were incidence of any stage ROP, severe ROP (defined as stage 3–5), and ROP requiring bevacizumab or surgical treatment. Because the interventions of interest could potentially impact mortality, we also collected data on in-hospital any-cause mortality.

We included comparative original studies (randomized or observational) and excluded single arm studies. Both randomized and observational studies were included in the analysis so as to capture all existing evidence on this question. When \( \geq 2 \) randomized controlled trials (RCTs) were available, a planned subgroup analysis of only the RCTs was performed. We could then determine whether the outcome effect persisted when the lesser quality evidence was excluded from the analysis.

Data Extraction

Reviewers extracted data independently from the included studies in duplicates, using a standardized, piloted, Web-based form that was developed based on the protocol. Data extracted included: demographics of participants, patient inclusion criteria, study design, intervention criteria, study design, intervention details, and outcomes of interest. For all outcomes, we extracted dichotomous data whenever available including number of patients with any stage ROP, severe ROP, ROP requiring treatment, and in-hospital mortality, as well as total numbers in each arm. When this data were not available, we used the effect measures reported by the individual studies (relative risks, odds ratios) along with the corresponding 95% confidence intervals (CIs) for the meta-analysis. Outcome data were extracted at the last follow-up reported. All disagreements or differences in extracted data were resolved by consensus.

Methodological Quality and Risk of Bias Assessment

Randomized trials were evaluated using the Cochrane risk of bias assessment tool.\textsuperscript{15} For every study,
the following was determined: how the randomization sequence was generated, whether allocation was concealed, who was blinded, the degree of loss of follow-up, and the nature of funding sources. Observational studies were evaluated using the Newcastle–Ottawa tool. This tool included the assessment of how the subjects represented the population of interest, how the comparative group was selected, how outcome was assessed, and the length and adequacy of follow-up when applicable. All discrepancies were resolved by a third reviewer with expertise in methodology.

**Statistical Analysis**

The reviewers extracted the contingency table data from the included studies to calculate the relative risks. We conducted a meta-analysis to pool relative risks using the random effect model to account for heterogeneity between studies as well as within-study variability. We used the I² statistic to estimate the percentage of total between-study variation due to heterogeneity rather than chance (ranging from 0% to 100%). I² values of 25%, 50%, and 75% are thought to represent low, moderate, and high heterogeneity, respectively. Statistical analyses were conducted through OpenMeta. All values are two-tailed and P < .05 was set as the threshold for statistical significance.

**RESULTS**

**Study Selection**

The flow diagram for study selection can be seen in Fig 1. From the database search and other sources, a total of 1479 records were identified for screening. Eighty-five studies were included in the qualitative analysis. We eventually identified 67 studies that provided quantitative data and they were included in the meta-analysis.

**Study Characteristics**

Twenty-seven studies on postnatal nutrition were included in the meta-analysis. These were further categorized into studies on the effect of human milk, early aggressive parenteral nutrition (PN), fish oil–based lipid emulsion, and dietary supplementation with vitamin A, vitamin E, inositol, and lutein. There were 17 studies on the management of supplemental oxygen, all of which addressed the effect of oxygen saturation targeting. A total of 18 studies on the effect of PRBC transfusions were analyzed. Five reports studied the effect of transfusion guidelines and the other 13 studied the effect of exogenous erythropoietin (EPO) on the risk of ROP. All 5 studies of infection prevention pertained to the effect of fluconazole prophylaxis.

**Risk of Bias Assessment**

The risk of bias evaluation of the included studies is summarized in Figs 2 and 3. For the 85 studies included in qualitative analysis, 55 were RCTs and 30 were observational studies. The included RCTs showed an overall medium risk of bias. Almost half of them were unblinded. The risk of bias assessment of the included observational studies showed low to medium risk of bias. These studies exhibited risk of bias in areas such as outcome assessment, follow-up sufficiency, and length of follow-up.

**Synthesis of Results**

**Postnatal Nutritional Interventions**

Increased use of human milk for enteral feeds did not reduce the
risk of any stage ROP. However, meta-analysis of 2 observational studies demonstrated a significant 60% reduction in severe ROP with increased human milk exposure (relative risk [RR] 0.39, 95% CI, 0.17–0.92; Fig 4, Table 1). Additionally, analysis of 2 studies on the use of an exclusive human milk–based diet suggested a reduced risk of death before discharge (RR 0.27, 95% CI, 0.08–0.96; Fig 4, Table 1).

When all study designs of early, aggressive PN were analyzed for effect on any stage ROP, there was no significant difference. However, analysis of the 2 RCTs on early, aggressive PN demonstrated a 78% risk reduction in any stage ROP when compared with more conservatively prescribed PN (RR 0.22, 95% CI, 0.09–0.55; Table 1). Aggressive PN did not have an effect on severe ROP or mortality. There was no change in the incidence of any stage ROP or severe ROP with use of a fish oil–based lipid emulsion for PN (Table 1).

Multiple nutritional supplements were also analyzed for their effects on ROP (Table 1). Vitamin A supplementation reduced the risk of any stage ROP by 33% (RR 0.67, 95% CI, 0.46–0.97; Fig 4, Table 1), but it had no effect on the incidence of severe ROP or mortality. Supplementation with vitamin E did not affect rates of any stage ROP. When analyzing both RCTs and observational studies, vitamin E supplementation was found to reduce the risk of developing severe ROP by 51% (RR 0.49, 95% CI, 0.25–0.98; Fig 4, Table 1). However, when the single observational study was removed and only the RCTs were analyzed, there was no longer a significant reduction in the risk of severe ROP (RR 0.52, 95% CI, 0.23–1.14). The 2 studies on lutein supplementation revealed no effect on the risk of any stage ROP, severe ROP, or death before discharge. The incidence of any stage ROP was not impacted by inositol supplementation. However, the 2 studies of inositol administration either as an intravenous medication or via formula feeds demonstrated a significantly reduced overall relative risk of severe ROP when compared with controls with no or minimal inositol exposure (RR 0.14, 95% CI, 0.03–0.69; Fig 4, Table 1).

Management of supplemental oxygen

Studies on the management of supplemental oxygen were primarily focused on oxygen saturation targeting (Table 2). Meta-analysis revealed that lower oxygen saturation targets, as defined by each study, resulted in a 14% reduction in the risk of developing any stage ROP (RR 0.86, 95% CI, 0.77–0.97; Fig 5, Table 2).

Fifteen studies of oxygen saturation targeting were analyzed for effect on severe ROP rates. When compared with higher oxygen saturation targets, lower oxygen saturation targets were associated with a 42% reduced risk of severe ROP or ROP requiring surgery (RR 0.58, 95% CI, 0.46–0.74; Fig 5, Table 2). When observational studies were excluded, analysis of the 4 RCTs demonstrated a nearly significant overall reduced risk of severe ROP for infants with oxygen saturation targets of 85% to 89% when compared with those with targets of 91% to 95% (RR of 0.72, 95% CI, 0.51–1.00; Fig 5, Table 2).
Human milk versus formula feeds and risk of severe ROP or ROP requiring treatment.

**Studies**

- Hylander 2001
  - Estimate (95% CI): 0.390 (0.129, 1.176)
  - Events (Ev): 4/84
  - Treatment (Trt): 11/90
- Maayan-Metzger 2012
  - Estimate (95% CI): 0.392 (0.103, 1.492)
  - Events (Ev): 3/188
  - Treatment (Trt): 7/172
- Overall (I² = 0%, P = 0.994)
  - Estimate (95% CI): 0.391 (0.167, 0.915)
  - Events (Ev): 7/272
  - Treatment (Trt): 18/262

Human milk versus formula feeds and risk of mortality before discharge.

**Studies**

- Sullivan 2010
  - Estimate (95% CI): 0.300 (0.074, 1.219)
  - Events (Ev): 3/138
  - Control (Ctrl): 5/69
- Cristofalo 2013
  - Estimate (95% CI): 0.167 (0.008, 3.313)
  - Events (Ev): 0/29
  - Control (Ctrl): 2/24
- Overall (I² = 0%, P = 0.727)
  - Estimate (95% CI): 0.270 (0.076, 0.940)
  - Events (Ev): 3/167
  - Control (Ctrl): 7/93

Aggressive TPN versus standard care and risk of any stage ROP. RCTs only.

**Studies**

- Can 2013
  - Estimate (95% CI): 0.159 (0.038, 0.669)
  - Events (Ev): 2/40
  - Control (Ctrl): 11/35
- Drenckpohl 2008
  - Estimate (95% CI): 0.271 (0.081, 0.902)
  - Events (Ev): 3/48
  - Control (Ctrl): 12/52
- Overall (I² = 0%, P = 0.578)
  - Estimate (95% CI): 0.218 (0.086, 0.547)
  - Events (Ev): 5/88
  - Control (Ctrl): 23/87

Vitamin A supplementation and risk of any stage ROP.

**Studies**

- Marxer 2012
  - Estimate (95% CI): 0.879 (0.449, 1.720)
  - Events (Ev): 11/42
  - Control (Ctrl): 14/47
- Shenai 1987
  - Estimate (95% CI): 0.439 (0.191, 1.009)
  - Events (Ev): 5/19
  - Control (Ctrl): 12/20
- Ubers 2014
  - Estimate (95% CI): 0.665 (0.389, 1.135)
  - Events (Ev): 14/60
  - Control (Ctrl): 33/94
- Overall (I² = 0%, P = 0.444)
  - Estimate (95% CI): 0.467 (0.459, 0.969)
  - Events (Ev): 30/121
  - Control (Ctrl): 59/161

Vitamin E supplementation and risk of severe ROP or ROP requiring treatment.

**Studies**

- Johnson 1989
  - Estimate (95% CI): 0.346 (0.096, 1.261)
  - Events (Ev): 3/208
  - Control (Ctrl): 9/216
- Phelps 1987
  - Estimate (95% CI): 1.403 (0.590, 3.338)
  - Events (Ev): 11/97
  - Control (Ctrl): 8/99
- Finer 1983
  - Estimate (95% CI): 0.249 (0.064, 0.970)
  - Events (Ev): 3/65
  - Control (Ctrl): 8/27
- Hitner 1983
  - Estimate (95% CI): 0.296 (0.060, 1.463)
  - Events (Ev): 2/69
  - Control (Ctrl): 5/51
- Finer-2 1982
  - Estimate (95% CI): 0.531 (0.102, 2.765)
  - Events (Ev): 2/48
  - Control (Ctrl): 4/51
- Pukin 1981
  - Estimate (95% CI): 1.000 (0.020, 49.110)
  - Events (Ev): 0/37
  - Control (Ctrl): 0/37
- Hitner-2 1981
  - Estimate (95% CI): 0.993 (0.005, 1.433)
  - Events (Ev): 0/60
  - Control (Ctrl): 5/61
- Overall (I² = 29%, P = 0.209)
  - Estimate (95% CI): 0.488 (0.244, 0.976)
  - Events (Ev): 21/574
  - Control (Ctrl): 36/532

Inositol supplementation and risk of severe ROP or ROP requiring treatment.

**Studies**

- Friedman 2000
  - Estimate (95% CI): 0.196 (0.027, 1.441)
  - Events (Ev): 1/24
  - Control (Ctrl): 10/47
- Hallman 2002
  - Estimate (95% CI): 0.063 (0.004, 1.083)
  - Events (Ev): 0/114
  - Control (Ctrl): 7/107
- Overall (I² = 0%, P = 0.521)
  - Estimate (95% CI): 0.135 (0.026, 0.590)
  - Events (Ev): 1/138
  - Control (Ctrl): 17/154

**FIGURE 4**

Forest plots for significant analyses of postnatal nutritional interventions. Ctrl, control group; Ev, events; Trt, treatment group.
<table>
<thead>
<tr>
<th>Intervention Category</th>
<th>No. of Studies</th>
<th>Study Ref.</th>
<th>Overall RR</th>
<th>95% CI</th>
<th>Intervention n/N</th>
<th>Control n/N</th>
<th>Overall I² (%)</th>
<th>P Value</th>
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<td>21–25</td>
<td>0.86</td>
<td>0.72–1.04</td>
<td>138/471</td>
<td>152/442</td>
<td>0</td>
<td>0.48</td>
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<td>2</td>
<td>23, 24</td>
<td>1.07</td>
<td>0.76–1.49</td>
<td>64/167</td>
<td>32/93</td>
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<td>0.65</td>
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<td>Severe ROP</td>
<td>2</td>
<td>22, 25</td>
<td>0.39</td>
<td>0.17–0.92</td>
<td>7/272</td>
<td>18/262</td>
<td>0</td>
<td>0.99</td>
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<tr>
<td>Mortality</td>
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<td>23, 24</td>
<td>0.27</td>
<td>0.08–0.96</td>
<td>3/167</td>
<td>7/93</td>
<td>0</td>
<td>0.73</td>
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<td><strong>Aggressive PN</strong></td>
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<tr>
<td>Any ROP</td>
<td>3</td>
<td>26, 28, 29</td>
<td>0.41</td>
<td>0.11–1.52</td>
<td>15/137</td>
<td>28/119</td>
<td>72</td>
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<tr>
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<td>26, 29</td>
<td>0.22</td>
<td>0.09–0.55</td>
<td>5/88</td>
<td>23/87</td>
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<td>2/184</td>
<td>4/135</td>
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<td>0.75</td>
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<td>27, 29</td>
<td>0.78</td>
<td>0.09–7.05</td>
<td>17/193</td>
<td>8/100</td>
<td>57</td>
<td>0.13</td>
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<tr>
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<td>2</td>
<td>30, 31</td>
<td>0.42</td>
<td>0.08–2.51</td>
<td>15/80</td>
<td>29/84</td>
<td>80</td>
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<td>0.11–1.91</td>
<td>4/80</td>
<td>13/84</td>
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<td>32, 33</td>
<td>1.22</td>
<td>0.59–2.65</td>
<td>11/96</td>
<td>9/97</td>
<td>0</td>
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<td>4</td>
<td>32–35</td>
<td>0.80</td>
<td>0.55–1.18</td>
<td>33/198</td>
<td>48/239</td>
<td>0</td>
<td>0.42</td>
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<tr>
<td><strong>Vitamin E</strong></td>
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<td></td>
</tr>
<tr>
<td>Any ROP</td>
<td>8</td>
<td>38–43</td>
<td>0.96</td>
<td>0.85–1.08</td>
<td>255/638</td>
<td>264/682</td>
<td>0</td>
<td>0.48</td>
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<td>38–39, 41–43</td>
<td>0.97</td>
<td>0.84–1.12</td>
<td>214/589</td>
<td>231/551</td>
<td>7</td>
<td>0.38</td>
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<td>36, 37, 39–43</td>
<td>0.49</td>
<td>0.24–0.98</td>
<td>21/574</td>
<td>36/532</td>
<td>29</td>
<td>0.21</td>
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<td>RCT only</td>
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<td>36, 37, 39, 41–43</td>
<td>0.52</td>
<td>0.23–1.14</td>
<td>19/505</td>
<td>31/481</td>
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<tr>
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<td>38, 41, 42</td>
<td>0.75</td>
<td>0.48–1.23</td>
<td>31/149</td>
<td>44/158</td>
<td>32</td>
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<td><strong>Lutein</strong></td>
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<td>48, 47</td>
<td>0.89</td>
<td>0.59–1.32</td>
<td>33/144</td>
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<td>0.70</td>
<td>0.30–1.61</td>
<td>9/144</td>
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<td>48, 47</td>
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<tr>
<td>Any ROP</td>
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<td>44, 45</td>
<td>0.85</td>
<td>0.42–1.72</td>
<td>24/138</td>
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<td>44, 45</td>
<td>0.14</td>
<td>0.05–0.68</td>
<td>1/138</td>
<td>17/154</td>
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<td>44, 45</td>
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<td>0.17–5.69</td>
<td>16/138</td>
<td>28/154</td>
<td>74</td>
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Analysis of 8 studies on oxygen saturation targeting revealed lower oxygen saturation targets (as defined by each study) increased the risk of death before discharge by 15% (RR 1.15, 95% CI, 1.04–1.29; Fig 5, Table 2). This finding remained significant when the 4 RCTs comparing oxygen saturation targets of 85% to 89% to targets of 91% to 95% were analyzed (RR 1.17, 95% CI, 1.03–1.32; Fig 5, Table 2).

Management of Red Blood Cell Transfusions

Studies on the management of PRBC transfusions focused on 2 primary interventions: the use of hemoglobin transfusion guidelines and administration of EPO (Table 3). The use of more restrictive, hemoglobin-based PRBC transfusion guidelines did not significantly affect the risk of any stage ROP (RR 0.99, 95% CI, 0.77–1.25), severe ROP (RR 1.02, 95% CI, 0.68–1.53 for RCTs only), or death before discharge (RR 1.27, 95% CI, 0.88–1.84) when compared with standard care or more liberal guidelines. The administration of EPO did not influence the risk of any stage ROP (RR 1.09, 95% CI, 0.91–1.30), severe ROP (RR 1.13, 95% CI, 0.77–1.64), or mortality (RR 0.94, 95% CI, 0.69–1.29) when all study designs were analyzed. This held true when the meta-analysis was limited to only RCTs. Similarly, subgroup analysis based on the timing of the first dose of EPO (early EPO defined as first dose given at <8 days of life and late EPO defined as first dose given at >8 days of life) failed to demonstrate an impact on any of the outcomes analyzed.

Interventions for Infection Reduction

There were 9 studies on the effect of infection reduction interventions on rates of ROP; however, only those on fluconazole prophylaxis for the prevention of fungal infection had a sufficient number of studies to allow for quantitative analysis (Table 4). No studies reported rates of any stage ROP. Meta-analysis of 4 studies demonstrated no significant effect of fluconazole prophylaxis on the risk of developing severe ROP or ROP requiring surgery (RR 0.82, 95% CI, 0.62–1.10). Fluconazole prophylaxis did not affect rates of death before hospital discharge (RR 0.85, 95% CI, 0.63–1.14). Findings were similar when only the 4 RCTs were analyzed (RR 0.83, 95% CI, 0.60–1.15).

DISCUSSION

Summary of Evidence

Although there are few, focused systematic reviews on the prevention of ROP, this is the first comprehensive meta-analysis of interventions aimed at multiple modifiable risk factors thought to be associated with an increased incidence of ROP. Our review revealed multiple subcategories of postnatal nutritional interventions. Meta-analysis of 2 cohort studies on the effect of breast milk versus formula feeds found a 60% reduction in the risk of severe ROP. This favorable finding was complicated by the need to categorize intervention and control groups as only or mainly breast milk fed compared with only or mainly infant formula fed, respectively. This classification was necessary because of the variability between studies in reporting enteral feed type, volume, exclusivity, duration, etc. The intervention group in the study by Hylander et al received 20% to 100% human milk feeding whereas the control group was exclusively formula fed. Comparatively, the Maayan-Metzger et al intervention group received at least 5 of 8 meals as human milk during the first month of life, whereas the control group received ≤3 human milk feeds. We also found that an exclusive human milk diet may have a favorable effect on the risk of mortality before discharge for preterm infants. The 2 RCTs of
Lower O₂ saturation target versus higher O₂ saturation target (as defined by each study) and risk of any stage ROP.

Studies
- Schmidt 2013
- Di Fiore 2012
- Booth II 2013

Estimate (95% CI)  Ev/Trt  Ev/Ctrl

Schmidt 2013 0.976 (0.708, 1.344) 64/500 66/503
Di Fiore 2012 0.728 (0.329, 1.162) 9/49 13/58
Booth II 2013 0.787 (0.423, 0.994) 110/1035 141/1044

Overall (I² = 67%, P < 0.001) 0.575 (0.447, 0.739) 357/3951 598/4156

O₂ saturation target of 85% to 89% versus 91% to 95% and risk of severe ROP or ROP requiring treatment. RCTs only.

Studies
- Schmidt 2013
- Di Fiore 2012
- Booth II 2013

Estimate (95% CI)  Ev/Trt  Ev/Ctrl

Schmidt 2013 0.976 (0.708, 1.344) 64/500 66/503
Di Fiore 2012 0.728 (0.329, 1.162) 9/49 13/58
Booth II 2013 0.787 (0.423, 0.994) 110/1035 141/1044

Overall (I² = 71.9%, P < 0.016) 0.715 (0.515, 1.004) 223/2328 311/2287

Lower O₂ saturation target versus higher O₂ saturation target (as defined by each study) and mortality before discharge.

Studies
- Schmidt 2013
- Di Fiore 2012
- Booth II 2013

Estimate (95% CI)  Ev/Trt  Ev/Ctrl

Schmidt 2013 1.097 (0.841, 1.430) 97/402 88/599
Di Fiore 2012 1.578 (0.371, 6.714) 4/49 3/58
Booth II 2013 1.167 (0.597, 2.317) 231/1221 203/1220

Overall (I² = 6%, P < 0.984) 1.154 (1.036, 1.286) 567/3179 528/3425

O₂ saturation target of 85% to 89% versus 91% to 95% and risk of mortality before discharge. RCTs only.

Studies
- Schmidt 2013
- Di Fiore 2012
- Booth II 2013

Estimate (95% CI)  Ev/Trt  Ev/Ctrl

Schmidt 2013 1.097 (0.841, 1.430) 97/402 88/599
Di Fiore 2012 1.578 (0.371, 6.714) 4/49 3/58
Booth II 2013 1.167 (0.597, 2.317) 231/1221 203/1220

Overall (I² = 0%, P < 0.990) 1.164 (1.032, 1.316) 664/5026 605/5259

FIGURE 5
Forest plots for significant analyses of oxygen saturation targeting. Ctrl, control group; EV, events; Trt, treatment.
exclusive human milk feedings that used a human milk–based fortifier demonstrated a significant overall reduced relative risk of mortality equal to 0.27.

The 2 RCTs of early, aggressive PN demonstrated a significant 80% reduction in any stage ROP. Although the trials were analyzed together because both studied early, aggressive PN, the exact PN strategy was different between the 2 studies. Can et al studied the effect of both increased early amino acid and fat emulsion administration. Drenckpohl et al, on the other hand, studied the effect of only increased early fat emulsion (initial amino acid delivery was 3 g/kg per day in both experimental and control groups with a goal of 3.5 g/kg per day). However, evidence suggests that early, aggressive PN is safe, so the potential benefit of this intervention outweighs any known risks.

Vitamin A supplementation via intramuscular injection reduced the rate of any stage ROP by 30%. However, the dosing regimen used in the 3 studies analyzed was variable, making clinical application challenging. Additionally, vitamin A injection may not be a reliable means of ROP prevention because it was not commercially available during the 4-year shortage (late 2010 to July 2014). Although its again on the market, the estimated cost of injectable vitamin A has increased substantially from $18 per vial before the shortage to $1100 per vial after the shortage (K.K. Graner, RPh., personal communication, 2015), arguably making it a cost-prohibitive ROP prevention strategy.

Analysis of vitamin E and inositol suggested that these supplements may reduce the risk of severe ROP by 50%. However, this positive effect may reduce the risk of severe ROP by 50%. However, this positive effect may reduce the risk of severe ROP by 50%. However, this positive effect may reduce the risk of severe ROP by 50%. However, this positive effect may reduce the risk of severe ROP by 50%

## Table 3: Meta-analysis of Management of PRBC Transfusions

<table>
<thead>
<tr>
<th>Intervention Category</th>
<th>No. of Studies</th>
<th>Study Ref.</th>
<th>Overall RR</th>
<th>95% CI</th>
<th>Intervention n/N</th>
<th>Control n/N</th>
<th>Overall P (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any ROP</td>
<td>3</td>
<td>65–67</td>
<td>0.99</td>
<td>0.77–1.25</td>
<td>45/92</td>
<td>50/94</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>Severe ROP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>5</td>
<td>10, 65–68</td>
<td>0.78</td>
<td>0.48–1.24</td>
<td>70/1550</td>
<td>97/1527</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>RCTs only</td>
<td>4</td>
<td>65–68</td>
<td>1.02</td>
<td>0.68–1.53</td>
<td>40/315</td>
<td>41/322</td>
<td>0.68</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>4</td>
<td>65–68</td>
<td>1.27</td>
<td>0.88–1.84</td>
<td>53/315</td>
<td>41/322</td>
<td>0.69</td>
<td></td>
</tr>
<tr>
<td>All EPO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ROP</td>
<td>9</td>
<td>69–71, 73, 75–78, 81</td>
<td>1.09</td>
<td>0.91–1.30</td>
<td>297/818</td>
<td>233/714</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Severe ROP</td>
<td>8</td>
<td>69, 71, 73, 75–78, 81</td>
<td>1.11</td>
<td>0.86–1.42</td>
<td>213/680</td>
<td>152/576</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td>All studies</td>
<td>9</td>
<td>69–74, 78–80</td>
<td>1.13</td>
<td>0.77–1.64</td>
<td>76/728</td>
<td>69/723</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>RCTs only</td>
<td>8</td>
<td>69, 71–74, 78–80</td>
<td>1.18</td>
<td>0.70–1.97</td>
<td>50/590</td>
<td>42/587</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>10</td>
<td>69–71, 74, 75, 77–81</td>
<td>0.94</td>
<td>0.69–1.29</td>
<td>76/911</td>
<td>69/830</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>All EPO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ROP</td>
<td>7</td>
<td>69–71, 76–80</td>
<td>1.06</td>
<td>0.92–1.23</td>
<td>179/487</td>
<td>165/448</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Severe ROP</td>
<td>6</td>
<td>69–71, 72, 78–79</td>
<td>0.99</td>
<td>0.69–1.41</td>
<td>52/509</td>
<td>55/502</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>8</td>
<td>69–71, 75, 77–81</td>
<td>0.93</td>
<td>0.67–1.29</td>
<td>67/773</td>
<td>63/892</td>
<td>0.93</td>
<td></td>
</tr>
<tr>
<td>Late EPO</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any ROP</td>
<td>2</td>
<td>73, 77</td>
<td>1.23</td>
<td>0.57–2.98</td>
<td>84/189</td>
<td>63/186</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Severe ROP</td>
<td>3</td>
<td>73, 74, 80</td>
<td>1.64</td>
<td>0.72–3.75</td>
<td>24/219</td>
<td>14/223</td>
<td>0.30</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>3</td>
<td>74, 77, 80</td>
<td>1.00</td>
<td>0.47–2.10</td>
<td>12/178</td>
<td>12/179</td>
<td>0.80</td>
<td></td>
</tr>
</tbody>
</table>

Early EPO: first dose given before the eighth day of life; late EPO: first dose given on or after the eighth day of life.
was no longer significant when the single cohort study\textsuperscript{40} was removed and only the RCTs were analyzed. In addition, 3 of the studies used intravenous vitamin E. Caution may be warranted when prescribing intravenous vitamin E to preterm infants because previous evidence has raised concern for an increased risk of sepsis with this route of administration.\textsuperscript{93}

Inositol is a nonglucose carbohydrate that may play an important role in early development and is involved in cell signaling, neuronal development, and pulmonary surfactant production.\textsuperscript{94} For reference, the average concentration of inositol in preterm milk is \( \sim 1350 \mu\text{mol} / \text{L} \) (or 240 mg/L).\textsuperscript{95} The commonly prescribed preterm infant formulas currently in use contain 280 to 350 mg/L of inositol.\textsuperscript{96–98} Analysis of the single cohort study\textsuperscript{44} and 1 RCT\textsuperscript{45} of inositol supplementation revealed a significantly reduced overall relative risk of severe ROP. In the first study, Friedman et al\textsuperscript{44} studied the effect of a high inositol infant formula (2500 \( \mu\text{mol} / \text{L} \) or 450 mg/L) on rates of severe ROP. The second study by Hallman et al\textsuperscript{45} supplemented neonates in the intervention group with intravenous inositol (80 mg/kg per day for the first 5 days of life). Although this limited meta-analysis of 2 studies suggests that inositol could positively affect rates of severe ROP, additional data should be forthcoming in the next 2 to 5 years. The Eunice Kennedy Shriver National Institute of Child Health and Human Development is currently recruiting participants for a phase 3, randomized, placebo-controlled study to determine the effectiveness of myo-inositol injection on increasing the incidence of survival without severe ROP in preterm neonates <28 weeks gestation (www.clinicaltrials.gov, identifier NCT01954082).\textsuperscript{99}

Our quantitative meta-analysis of supplemental oxygen management focused on the effect of oxygen saturation targets on rates of ROP. Lower oxygen saturation targets, as defined by each study, reduced the rate of any stage ROP by nearly 15% when all study designs were analyzed.\textsuperscript{48,50,52,54,56, 57,60,61} Interestingly, studies in the United States\textsuperscript{20,52,56, 57,60,61} showed a significant reduction in any stage ROP with lower oxygen saturation targets (RR 0.78, 95% CI, 0.68–0.88), whereas this effect was not significant in other countries.\textsuperscript{48,54}

Fifteen cohort studies and RCTs studying oxygen saturation targeting reported rates of severe ROP or ROP requiring intervention.\textsuperscript{48,49,51, 53–64} By incorporating the cohort studies into the meta-analysis, >8000 preterm neonates were included. Approximately half of the preterm neonates were enrolled in a randomized, controlled trial.\textsuperscript{48,53,63, 64} The remaining 46% were part of a cohort study that frequently involved investigating ROP outcomes after a change in clinical management of supplemental oxygen.\textsuperscript{49,51,54–62} In these studies, the definition of “lower oxygen saturation target” varied from a low of 70% to 90%\textsuperscript{62} to a high of 90% to 96%.\textsuperscript{58} The definition of “higher oxygen saturation target” ranged from a low of 88% to 96%\textsuperscript{49} to a high of 95% to 100%.\textsuperscript{56} Based on our meta-analysis, the risk of severe ROP or ROP requiring intervention was reduced by 40% using lower oxygen saturation targets as defined by each study.

However, this approach to oxygen management appears to be associated with undesirable effects on mortality before hospital discharge. When all study types were analyzed, we found an unacceptable 15% increased risk of mortality before discharge with lower oxygen saturation targets. Interestingly, 9\textsuperscript{49–52,54,55,58,60,62} of the 13 cohort studies did not report in-hospital mortality rates as an additional outcome.

<table>
<thead>
<tr>
<th>TABLE 4 Meta-analysis of Infection Prevention</th>
<th>Control n/N</th>
<th>Intervention n/N</th>
<th>Overall RR</th>
<th>95% CI</th>
<th>Overall I\textsuperscript{2} (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole prophylaxis</td>
<td>81/547</td>
<td>76/527</td>
<td>0.82</td>
<td>0.62–1.0</td>
<td>0</td>
<td>0.45</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.69</td>
</tr>
<tr>
<td>Mortality</td>
<td>82–85</td>
<td>82–85</td>
<td>0.85</td>
<td>0.85–1.15</td>
<td>0.85</td>
<td>0.35</td>
</tr>
<tr>
<td>All studies</td>
<td>82–85</td>
<td>82–85</td>
<td>0.85</td>
<td>0.85–1.15</td>
<td>0.85</td>
<td>0.35</td>
</tr>
<tr>
<td>RCT only</td>
<td>82–85</td>
<td>82–85</td>
<td>0.85</td>
<td>0.85–1.15</td>
<td>0.85</td>
<td>0.35</td>
</tr>
</tbody>
</table>
Analysis limited to the 4 RCTs\textsuperscript{48, 53, 63, 64} again demonstrated a 17% increased risk of in-hospital mortality for those infants with a lower oxygen saturation target (85–90%) when compared with those with a higher oxygen saturation target (91–95%). Our overall relative risk of in-hospital mortality (RR 1.17) is lower than that reported in the NEOPROM collaborative study\textsuperscript{8} (RR 1.41, 95% CI, 1.14–1.74). In the NEOPROM study, only the infants monitored with the revised oximeter calibration algorithm were included in their death at discharge analysis. These infants may have spent more time in the intended lower oxygen saturation range resulting in a greater increased risk of death.

We also evaluated ROP outcomes for interventions aimed at managing PRBC transfusions: primarily the use of hemoglobin transfusion guidelines and administration of EPO. However, we found no significant impact of either intervention on rates of any stage ROP, severe ROP, or ROP requiring intervention. Although our meta-analysis includes additional recently available studies, the findings are similar to previously published Cochrane reviews.\textsuperscript{100–102}

There is very little literature published on reducing the risk of infection in preterm neonates and its effect on the incidence of ROP. Although there are single studies of interventions to prevent infection that also report ROP outcomes,\textsuperscript{103–105} only those studying fluconazole prophylaxis had sufficient numbers for quantitative analysis. Despite a reduced risk of invasive fungal infection, fluconazole prophylaxis has no significant effect on the risk of developing severe ROP.

**Limitations**

The greatest limitation of this meta-analysis is the overall absence of large, well-designed clinical studies in the literature. Approximately 75 000 neonates are born at <32 completed weeks of gestation each year in the United States,\textsuperscript{106} and ROP is one of the key morbidities that can lead to long-term neurodevelopmental impairment in these infants. The results of this study suggest that there is a significant need for enhanced translational and clinical research to better understand how ROP can safely be prevented in very preterm neonates.

Among the studies included in this meta-analysis, the format for reporting ROP outcomes was highly variable (eg, by stage, type, prethreshold/threshold, need for surgery, etc). To address this issue, we analyzed ROP outcomes using 2 categories: (1) presence of any stage ROP, and (2) ROP that was likely to result in an unfavorable visual outcome. An undesirable retinal outcome included patients with severe ROP (stage ≥3), type 1 threshold ROP, or ROP requiring medical or surgical intervention. If a single study reported undesirable retinal outcomes in multiple formats, the rate of severe ROP was used to provide increased sensitivity and similarity between articles. The use of common standards for ROP outcomes research is needed.

This meta-analysis was also limited by the heterogeneity of interventions even within categories as previously described (eg, variation in vitamin and medication dosages/regimens, parenteral and enteral feeding strategies, definition of oxygen saturation targets, hemoglobin transfusion guidelines, etc). However, study characteristics were thoughtfully reviewed before the meta-analyses in an effort to provide a meaningful synthesis of the current evidence on the prevention of ROP to guide care of the preterm infant.

**CONCLUSIONS**

The results of this meta-analysis suggest that vitamin A supplementation and early, aggressive PN may reduce any stage ROP in preterm infants. Risk of severe ROP or ROP requiring surgery may be reduced with breast milk feedings, vitamin E supplementation, and inositol therapy. Although lower oxygen saturation targets reduce the risk of both any stage and severe ROP, this approach to oxygen management should be approached with caution given concerns about potential adverse effects on mortality before discharge. Transfusion guidelines, use of early or late EPO, and fluconazole prophylaxis do not affect the risk of developing ROP. Continued work is needed to identify additional practice management strategies and medical therapies for the prevention of ROP in at-risk preterm neonates.

**ACKNOWLEDGMENTS**

We thank the Mayo Clinic Quality Academy and the Robert D. and Patricia E. Kern Center for the Science of Health Care Delivery for supporting this study.

**ABBREVIATIONS**

CI: confidence interval
EPO: erythropoietin
PN: parenteral nutrition
PRBC: packed red blood cell
RCT: randomized controlled trial
ROP: retinopathy of prematurity
RR: relative risk
VLBW: very low birth weight
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Interventions To Prevent Retinopathy of Prematurity: A Meta-analysis
Jennifer L. Fang, Atsushi Sorita, William A. Carey, Christopher E. Colby, M. Hassan Murad and Fares Alahdab
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