High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis

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CRD summary
The review concluded that in pre-term infants of less than 33 weeks gestational age, early low oxygen and late high oxygen saturation was associated with a reduced risk for severe retinopathy of prematurity, but further research is needed. The potential for biases in the review, plus uncertain quality and variation of included studies, limits the reliability of the authors' conclusions.

Authors' objectives
To explore the association between severe retinopathy of prematurity incidence of premature infants with high or low oxygen saturation measured by pulse oximetry.

Searching
PubMed and EMBASE were searched to May 2009 for articles published in English. Search terms were reported. Reference lists of retrieved articles were also searched.

Study selection
Randomised controlled trials (RCTs) and cohort studies of the association between oxygen saturation (measured by oximetry) and retinopathy of prematurity in infants with a gestational age at birth of 32 weeks or less were eligible for inclusion. Relevant outcomes were retinopathy of prematurity (grade three or higher), pre-threshold or threshold retinopathy of prematurity, cryotherapy for retinopathy of prematurity, or supplemental therapeutic oxygen for pre-threshold retinopathy of prematurity (definitions reported in review).

The included studies examined low oxygen saturation (70 to 96%) with high oxygen saturation (85 to 100%) in infants in the first several postnatal weeks or in infants after a postmenstrual age of at least 32 weeks. In the first weeks after birth studies, the oxygen timing ranged from birth to the first eight weeks (early oxygen); for the postmenstrual age studies, oxygen timing ranged from 32 to 42 weeks (late oxygen). A small number of studies reported developmental outcomes and mortality. Birth weight in the first few postnatal weeks ranged from 500 to 1500g, and in postmenstrual age from 726 to 986g (where reported).

The authors did not state how many reviewers performed study selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Two reviewers independently extracted data on the risk of severe retinopathy of prematurity to calculate relative risks (RRs), and 95% confidence intervals (CIs). Disagreements were resolved by discussion. Authors of the included studies were contacted if the study was unclear.

Methods of synthesis
A random-effects meta-analysis was undertaken to calculate the pooled relative risks and 95% confidence intervals. Statistical heterogeneity was assessed using the $X^2$ test and the $I^2$ statistic.

Stratified analyses were conducted according to oxygen limits, mean postmenstrual age, duration of oxygen, and study design. Sensitivity analysis was undertaken omitting one study at a time.

Publication bias was assessed by Begg's funnel plot and Egger's test.

Results of the review
Ten studies were included in the review (n=3,088 infants). These included five studies of infants in the first few weeks after birth and five studies of infants at the postmenstrual age of 32 weeks or more. Four studies were prospective cohorts, three were retrospective cohorts, and two were RCTs.

**Infants in the first few weeks after birth (up to eight weeks):** There was a statistically significantly decreased risk of retinopathy of prematurity in infants with low oxygen saturation compared with high oxygen saturation during the first few postnatal weeks (RR 0.48, 95% CI 0.31 to 0.75; I²=26%; five studies). Stratified analyses indicated that a greater decrease in risk of retinopathy of prematurity was observed in studies that had a low oxygen limit of 83% or less (RR 0.34, 95% CI 0.18 to 0.65; two studies), but this was not statistically significantly different from studies with an oxygen lowest limit of 83% or more. Two studies that did not specify the oxygen duration did not show a statistically significant result. Three studies with duration of oxygen use for the first four or more postnatal weeks showed a statistically significant positive effect (RR 0.49, 95% CI 0.28 to 0.88).

**Infants with postmenstrual age of 32 weeks or more:** There was a statistically significantly decreased risk of retinopathy of prematurity in infants with high oxygen saturation compared with low oxygen saturation at a postmenstrual age of 32 weeks or more (RR 0.54, 95% CI 0.35 to 0.82; five studies). Stratified analyses indicated that a greater decrease in risk of retinopathy of prematurity was observed in studies that had a high oxygen limit of 98% or more (RR 0.27, 95% CI 0.14 to 0.50; two studies), which was statistically significant compared with studies with an oxygen saturation of 97% or less. A greater decrease was also observed in studies that included infants after a mean postmenstrual age of 36 weeks (RR 0.38, 95% CI 0.17 to 0.84; two studies), but this was not statistically significant compared with studies of infants with a postmenstrual age of 32 to 35 weeks. There was also a statistically significant difference in the results obtained for RCTs compared with observational studies, with trials showing less effect than cohort studies.

Sensitivity analysis did not statistically significantly alter the results.

There was no evidence of publication bias.

**Authors’ conclusions**
Among pre-term infants with a gestational age of 32 weeks or less, early low oxygen and late high oxygen saturation were associated with a reduced risk for severe retinopathy of prematurity compared with low oxygen alone, but further research is needed.

**CRD commentary**
Inclusion criteria for the review were clearly defined. Two relevant databases were searched. There was the risk of language bias as only English language articles were included. Publication bias was assessed and was not detected. Attempts were made to reduce reviewer error and bias during data extraction, but it was not clear if such attempts were used for study selection.

Trial quality assessment was not reported, so the quality of the included studies was unknown. Trials were pooled using meta-analysis, but statistical heterogeneity was not always reported. A stratification analysis was undertaken, which indicated differences between studies, notably trials and observational studies. The authors acknowledged the lack of data reported in individual studies, and the high level of heterogeneity (which may indicate that pooling of studies was not appropriate).

Overall, the potential for biases within the review, together with the uncertain quality and heterogeneity of the included studies, limit the reliability of the author’s conclusions.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that a sufficiently powered RCT on optimal oxygen delivery in the early and late stages of retinopathy of prematurity that also ensures long-term visual, pulmonary, and neurodevelopment follow-up is needed. Trials should adopt the postmenstrual age concept.
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