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Optimal Oxygenation of Extremely Low Birth Weight Infants: A Meta-Analysis and Systematic Review of the Oxygen Saturation Target Studies

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Key Words
Extremely low birth weight infants · Mortality · NEOPROM · Oxygen saturation · Retinopathy of prematurity · Bronchopulmonary dysplasia · Necrotizing enterocolitis

Abstract
Background: The optimal oxygen saturation for extremely low birth weight infants in the postnatal period beyond the delivery room is not known. ***Objectives:*** To summarize and discuss the results of the randomized trials, constituting the NEOPROM (Neonatal Oxygenation Prospective Meta-analysis) collaborative study, examining the effect of low versus high functional oxygen saturation targets in the postnatal period in premature infants with gestational age <28 weeks. ***Methods:*** A meta-analysis of SUPPORT (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial), the three BOOST II (Benefits of Oxygen Saturation Targeting) studies and the COT (Canadian Oxygen Trial) was performed including a total of 4,911 infants randomized to either a low (85–89%) or high (91–95%) functional oxygen saturation (SpO_2) within the first 24 h after birth. ***Results:*** Relative risks (RR; 95% CIs) comparing a low versus a high oxygen saturation target were 1.41 (1.14–1.74) for mortality at discharge or at follow-up, 0.74 (0.59–0.92) for severe retinopathy of prematurity, 0.95 (0.86–1.04) for physiologic bronchopulmonary dysplasia, 1.25 (1.05–1.49) for necrotizing enterocolitis, 1.02 (0.88–1.19) for brain injury, and 1.01 (0.95–1.08) for patent ductus arteriosus. RR >1.0 favors a high oxygen saturation. ***Conclusions:*** RRs for mortality and necrotizing enterocolitis are significantly increased and severe retinopathy of prematurity significantly reduced in low compared to high oxygen saturation target infants. There are no differences regarding physiologic bronchopulmonary dysplasia, brain injury or patent ductus arteriosus between the groups. Based on these results, it is suggested that functional SpO_2 should be targeted at 90–95% in infants with gestational age <28 weeks until 36 weeks' postmenstrual age. However, there are still several unanswered questions in this field.

Introduction

The optimal oxygenation of extremely low birth weight infants has been hidden in the dark. This is not only due to a lack of knowledge of which values to target but as much due to a lack of understanding of the many detrimental effects of oxygen on the immature newborn infant.

Retrolental fibroplasia (RLF) was first described in 1942, and by 1954 it was estimated that 10,000 infants had been blinded by this condition [1, 2]. The appearance of RLF in the 1940s taught the neonatal community slowly

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that oxygen could be toxic to the premature infant [3] and during the 1950s and 1960s an appropriate administration of oxygen was sought through randomized trials [4].

From the early 1970s, oxygen administration was better controlled by the advent of transcutaneous pO_2 electrodes and pulse oximetry, and many believed the problem with RLF was solved. However, during the 1970s and 1980s it became clear that RLF was a prevailing and perhaps an increasing phenomenon in the smallest babies. RLF is the end stage of retinopathy of prematurity (ROP) which has been the common name since the early 1980s. Approximately half of all babies with gestational age <28 weeks develop some stage of ROP. In the Swedish EXPRESS study, 1/3 of babies with gestational age <27 weeks developed severe (≥ stage 3) ROP. Severe bronchopulmonary dysplasia was reported in 25% of the Swedish immature babies [5].

In the 1980s and 1990s, a new awareness arose about the toxicity of oxygen through the understanding of oxidative stress and how this may affect especially the newborn and premature infant. The understanding that oxidative stress is not only caused by oxygen represented a fundamental leap forward [6]. A number of free radical generating systems were identified after we first understood the important role of the oxygen radical generating system hypoxanthine-xanthine oxidase as an explanation of reoxygenation injury [7–10].

At the turn of the century, two randomized studies were published indicating that the oxygen saturation target should be kept lower than previously in order to prevent injuries. The Supplemental Therapeutic Oxygen for Pretreshold Retinopathy of Prematurity (STOP ROP) trial randomized infants with prethreshold ROP to low (SpO_2 89–94%) or high (SpO_2 96–99%) oxygen targets. The high targets caused more pulmonary complications but no significant difference in the rate of progression to threshold ROP [11]. In the Benefits of Oxygen Saturation Targeting (BOOST) trial, infants <30 weeks' gestational age were randomized from 3 weeks or more after birth to target a low SpO_2 (91–94%) or high SpO_2 (95–98%) until they breathed air. A high oxygen saturation target increased the days of oxygen therapy and use of health care resources [12]. Because randomization occurred several weeks after birth in these two studies there was a need for studies randomizing infants already within the first day after birth.

A number of observational studies supported the concept of keeping the saturation low. Flynn et al. [13] showed in the early 1990s that a PaO_2 >80 mm Hg was associated with a higher incidence of ROP. Tin et al. [14] some years later demonstrated that babies in a unit utilizing low (70–90%) alarm limits for SpO_2 had significantly less severe ROP than a unit aiming at high (88–98%) SpO_2 alarm limits (6 vs. 27%). There were also less pulmonary problems in the low saturation unit. In the following years, several cohort studies all strongly indicated that a lower SpO_2 target is preferable compared with a high target [15–21]. We summarized these studies and found a more than 50% significant reduction in severe ROP and a 20–25% reduction in bronchopulmonary dysplasia (BPD)/chronic lung disease when the SpO_2 target was low compared to high [22]. No difference in mortality was detected by any of these studies including two systematic reviews and meta-analysis [22, 23].

High oxygen therefore seems to contribute to eye and lung injury in premature infants; hyperoxia is also a risk factor for cerebral palsy [24]. The time was therefore ripe to carry out larger, strictly randomized controlled trials (RCT) with the aim to answer the question: what is the optimal oxygen saturation target in extremely low birth weight infants in the postnatal period? In this article, the results of the collaborative studies collectively called NEOPROM (Neonatal Oxygenation Prospective Meta-anylis) are summarized, analyzed and discussed.

Materials and Methods

NEOPROM

Five multicenter studies with rather similar allocations and outcome measures were organized with the aim to answer whether extremely premature infants after delivery room handling should be kept at a low or a high oxygen saturation target. These studies are the SUPPORT trial (Surfactant, Positive Pressure and Pulse Oximetry Randomized Trial), the three BOOST II trials from the UK, Australia and New Zealand, and the Canadian Oxygen Trial (COT). In these 5 trials, premature infants <28 weeks' gestational age were randomized to low (85–89%) or high functional SpO_2 targets (91–95%). Because of the similarities between these trials, it was decided to combine all data in a final meta-analysis called the NEOPROM project [25]. However, in spite of the uniformity of the studies there are subtle differences between them, for instance in the SUPPORT trial randomization occurred within the first 2 h of life while in the COT and BOOST II trials randomization occurred within the first 24 h.

All these studies were blinded with the use of electronically altered pulse oximeters (Masimo Radical Pulse Oximeters) that showed functional saturation levels of 88–92% for both targets of oxygen saturation, with a maximum variation of 3%. Consequently, in the low saturation group a 3% higher value and in the high saturation group a 3% lower value was read at the screen (for instance a reading of 90% saturation corresponds to an actual value of 87% in the low saturation group and 93% in the high saturation group). The oxygen saturation readings gradually changed and reverted to actual values when it was less than 84% or higher than

96%. Primary outcome was death or severe neurosensory disability at 18–24 months of age (corrected for prematurity). Secondary outcomes included a number of well-known morbidities commonly affecting premature infants.

The SUPPORT was a part of the Neonatal Research Network of the Eunice Kennedy Shriver National institute of Child Health and Human Development in the USA aiming to enroll 1,310 infants from 23 centers [26]; clinical.trials.gov number is NCT00233324. Infants between 24 weeks and 0 days and 27 weeks and 6 days of gestational age were entitled to be enrolled, and this occurred by block randomization (sealed opaque envelopes) between February 2005 and February 2009. The babies were stratified according to centers and gestational age (24–25 vs. 26–27 weeks). The study was a so-called 2-by-2 factorial trial. In one part of the trial, babies were randomly assigned to either intubation in the delivery room and surfactant administration within 1 h, or nasal continuous positive pressure ventilation in the delivery room. In the other part of SUPPORT, babies were randomly assigned within 2 h of birth to a target range for oxygen saturation of 85–89 or 91–95%. Registration was continued until 36 weeks or until the infant was breathing ambient air and did not require ventilator support or CPAP for more than 72 h. Of the 3,546 infants assessed for eligibility only 1,316 underwent randomization. A follow-up study at 18–22 months of age was recently published [27].

The BOOST II trials were three independent studies in the UK, Australia and New Zealand. They sought to enroll 2,740 infants born before 28 weeks' gestation within 24 h after birth [28]. The Current Controlled Trials number is ISRCTN00842661. Australian New Zealand Clinical Trials Registry numbers are ACTRN12605000055606 and ACTRN12605000253606. Enrolment occurred in 54 centers from March 2008 to December 2010. Randomization occurred centrally by computer and separately for each trial. Allocation was continued until 36 weeks or if the infant was breathing air before that. Approximately halfway through the trial, oximeters in the UK and Australia studies were changed to oximeters with a new calibration algorithm. Investigators in the UK had discovered that the Masimo Radical Oximeters had a shift up in the calibration curve of between 87 and 90%. This reduced the frequency of displayed oxygen-saturation values ranging from 87 to 90% and caused values ranging from 87 to 96% to read 1–2% higher. The oximeters with the revised calibration algorithm improved oxygen saturation targeting with more time in the intended oxygen saturation range, with clearer separation in the oxygen saturations between the low and high oxygen target groups [29]. In December 2010, the data and safety monitoring committees performed an interim analysis. Among the infants monitored with the original oximeters there was no difference between the two groups in mortality (15.6 vs. 16.8% in the low and high saturation groups, respectively). However, in the infants having used the revised algorithm, infants in the low saturation target group had an increased rate of death at 36 weeks postconceptual age compared with the high saturation target group (21.8 vs. 13.3%) [30]. At that time, recruitment to the New Zealand study was finished and recruitment to the UK and Australia studies was closed. These two BOOST II studies were therefore aborted prematurely, the three studies ending up including 2,445 of the aimed 2,740 infants.

The COT trial planned to enroll 1,200 infants from 25 units predominately from Canada, but centers from Germany, Finland, Argentina and Israel also participated [31]; clinicalTrials.gov identifer is NCT00637169. Infants with gestational age of 23 weeks and 0 days through 27 weeks and 6 days were eligible for enrolment during the first 24 h after birth. Of the 2,416 eligible infants 1,201 were enrolled from December 2006 to August 2010. Randomization was computer generated and stratified by study center. Study oximetry was continued until 36 weeks even if an infant was not receiving supplemental oxygen. 1,201 infants were enrolled, of these 1,147 had adequate data for the analysis of the composite primary outcome.

There was a change in the pulse oximeter software as described for the BOOST II study between February and June 2009, approximately halfway through enrolment.

Outcome Measures

Table 1 lists the definitions of outcome measures in each of the 5 trials used in the present article. For SUPPORT, the composite primary outcome was death before discharge or severe ROP defined as threshold ROP, ophthalmologic surgery, or the use of bevacizumab treatment for retinopathy. BPD was defined as oxygen dependency at 28 days or need for more than 30% oxygen or positive airway pressure at 36 weeks. Necrotizing enterocolitis (NEC) was recorded in the SUPPORT trial if the stage was ≥2 and intraventricular hemorrhage (IVH) if the grade was ≥2.

For BOOST II studies, mortality was noted at discharge. Data beyond hospital discharge have not yet been published. Severe ROP was defined according to the early treatment of ROP criteria [32]. BPD was defined as need of oxygen supplementation to maintain an oxygen saturation of ≥90% for the UK trial. Data from the BOOST II UK only are therefore given for this outcome measure. NEC was recorded if requiring surgery or causing death. IVH was noted if the grade was ≥2.

For the COT trial, the primary outcome was death before the corrected age of 18 months or survival with one or more of the following: gross motor disability (level 2 or higher according to the Gross Motor Function Classification System = GMFC), cognitive or language delay (defined as score of 85 or less on the Bayley Scales for Infant and Toddler Development, ed. 3), severe hearing loss (prescription of hearing aids or cochlear implants), and bilateral blindness (corrected visual acuity <20/200 in the better eye). Severe ROP was defined as ROP stage >3, or if the infant received cryo- or laser therapy in at least one eye, or bevacizumab therapy. BPD was defined as in the SUPPORT trial. NEC was recorded if there was the presence of pneumatosis intestinalis, hebatobiliary gas, or free intraperitoneal air on radiography, needing surgery, or found at autopsy. The COT trial did not reveal IVH data only 'brain injury' defined as IVH grade 4, and/or cystic periventricular leukomalacia, porencephalic cysts and ventriculomegaly.

Statistics

We created a summary of the outcome variables mortality, severe ROP, BPD, NEC, 'brain injury', and patent ductus arteriosus comparing low versus high SpO_2 targets. The average of the natural logarithm of the observed relative risk (RR) was estimated and the RR from each study was weighted by the inverse of its variance. We used random effects models, which take into account variation within and between studies (heterogeneity), to compute the summary RRs [33]. A two-tailed $p < 0.05$ was considered statistically significant. Heterogeneity between studies

Table 1. Outcome variables

Outcome variable	SUPPORT	BOOST II	COT
Primary outcome	severe ROP/death before discharge	death or severe disability 18–24 months	death before 18 months or severe neurosensory outcome
Mortality	18–22 months	before discharge	before 18 months
Severe ROP	threshold ROP, eye surgery bevacizumab treatment	treatment (ETROP)	stage 4 or 5, cryotherapy/laser/ bevacizumab
BPD	physiologic	physiologic	physiologic
NEC	stage ≥2	surgery or death	pneumatosis/free air/surgery or death
Brain injury	IVH grade 3 or 4	IVH grade 3 or 4	IVH grade 4, cystic PVL/porencephalic cyst/ventriculomegaly
Patent ductus arteriosus	any therapy	any therapy	any therapy

ETROP = Early Treatment for Retinopathy of Prematurity Cooperative Group [32].

Table 2. Basic characteristics of enrolled infants

	SUPPORT		BOOST II		COT	
	low	high	low	high	low	high
Gestational age, weeks	26 (1)	26 (1)	26.0 (1.2)	26.0 (1.2)	25.6 (1.2)	25.6 (1.2)
Birth weight, g	836 (193)	825 (193)	826 (184)	837 (189)	827 (190)	844 (199)
Antenatal steroids, %	96.8	95.6	89.6	90.7	88.2	90.0
Number	654	662	1,224	1,224	578	569

Gestational ages in BOOST UK were mean (SD) 26.0 (1.3) vs. 26.0 (1.3) in the low and high saturation groups, respectively. For BOOST AU and BOOST NZ, the numbers are 26.0 (1.2) vs. 26.0 (1.2) weeks and 26.1 (1.2) vs. 26.1 (1.2) weeks.

Birth weight in BOOST UK were mean (SD) 818 (182) and 824 (188) g in the low and high saturation groups, respectively. For BOOST AU and BOOST NZ, the numbers are 817 (177) vs. 833 (190) g and 873 (202) vs. 884 (186) g.

was evaluated with Q and I^2 statistics [34]. For the Q statistic $p < 0.10$ was considered to indicate heterogeneity, as previously recommended [35]. I^2 is the amount of total variation that is explained by variation between studies (i.e. I^2 of 25, 50 and 75% indicate low, moderate and high heterogeneity, respectively). Publication bias was assessed with Egger's test [36]. Results are given as relative risk (RR) and 95% CI in parentheses. Data for separate studies as well as typical estimates for important outcome measures are presented. Results from the three BOOST II trials, BOOST UK, BOOST AU and BOOST NZ, are presented separately, if data are available, as well as combined. Mortality data obtained by using the revised algorithm are primarily presented; however, all data are also given in the text. For the other outcome variables, revision of the algorithm did not affect the results and, therefore, all data regarding these are given combined.

Results

In total, 4,911 infants were enrolled, 2,456 in the low saturation and 2,455 in the high saturation group. The basic clinical data for the trials are presented in table 2. The mean gestational ages were around 26 weeks and mean birth weights between 820 and 850 g. There was an exposure of antenatal steroid use between 90 and 96%.

Primary Outcome

The composite of death or severe neurosensory disability at 18–24 months has been published for the SUP-

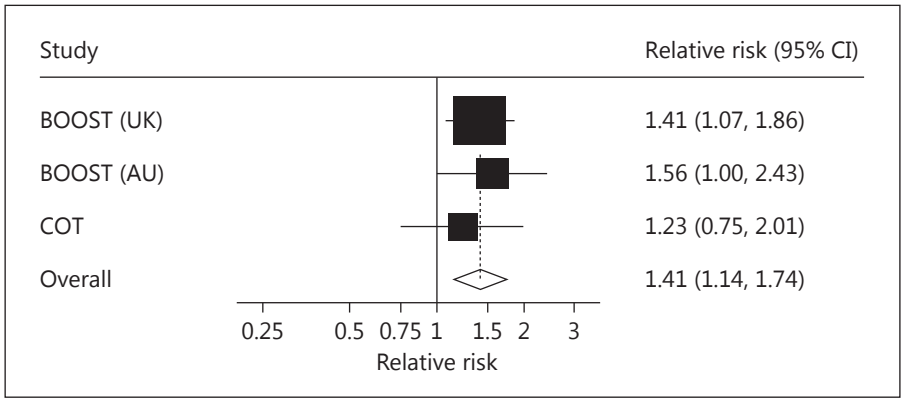

Fig. 1. Summary meta-analysis of mortality in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target. NEOPROM – revised algorithm. Data from revised software only.

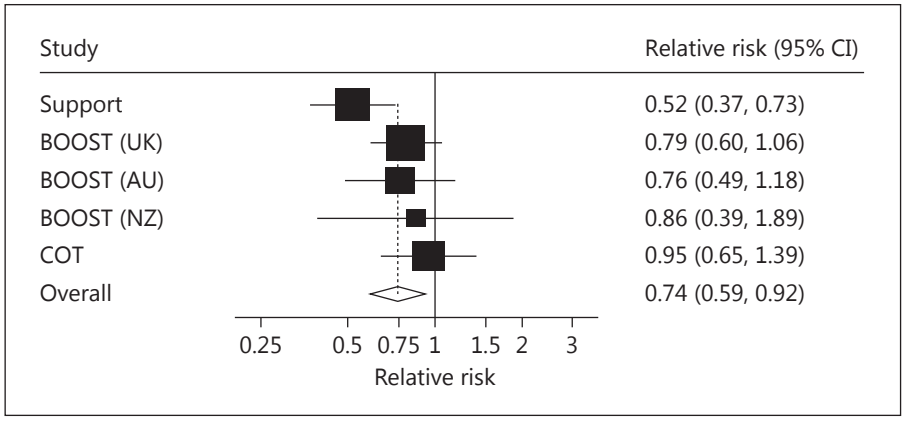

Fig. 2. Summary meta-analysis of severe ROP in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target.

PORT and COT trials only, showing no difference between the low and high saturation groups (SUPPORT 28.3 vs. 32.1%, COT 51.6 vs. 49.7%). Applying the revised software, death or disability in COT was found in 52.6% in the low and in 46.6% in the high saturation group, RR 1.30 (0.89–1.90).

Mortality

At 18–22 months corrected age [30] mortality for SUPPORT was 21.8 versus 18.2%, RR 1.25 (1.00–1.55), death before discharge in BOOST II (all included infants) was 19.2 versus 16.6%, RR 1.16 (0.98–1.37) (mortality at follow-up not reported) and for COT (death before 18 months) 16.6 versus 15.3%, RR 1.12 (0.78–1.61) in the low and high oxygen saturation groups, respectively.

Mortality data from infants measured with the revised software include part of the BOOST II UK and BOOST II AU trials as death at discharge and the COT trial as death before 18 months. RR for death was 1.41 (1.14–1.74) (>1 favoring the high saturation target group), I^2 = 0.0% (fig. 1). RR for death using data sampled with the original software is 1.04 (0.88–1.22).

For all studies, combined mortality was 19.3% in the low and 16.2% in the high saturation groups, respectively, giving a summary RR = 1.18 (1.04–1.34), I^2 = 0%, $p_{heterogeneity}$ = 0.83 (online supplementary fig. 1 and 2; see www.karger.com/doi/10.1159/000356561 for all online suppl. material).

Morbidities

Severe ROP was significantly reduced in the low saturation arm in the SUPPORT trial 8.6 versus 17.9%, RR 0.52 (0.37–0.73). When combining the three BOOST II trials severe ROP was found in 10.6 and 13.5% (RR 0.79, 0.63–1.00) in the low and high saturation groups, and in COT 12.8% in the low versus 13.1% in the high saturation groups, RR 0.95 (0.65–1.39). In the 5 trials, combined severe ROP was detected in 10.7% in the low saturation

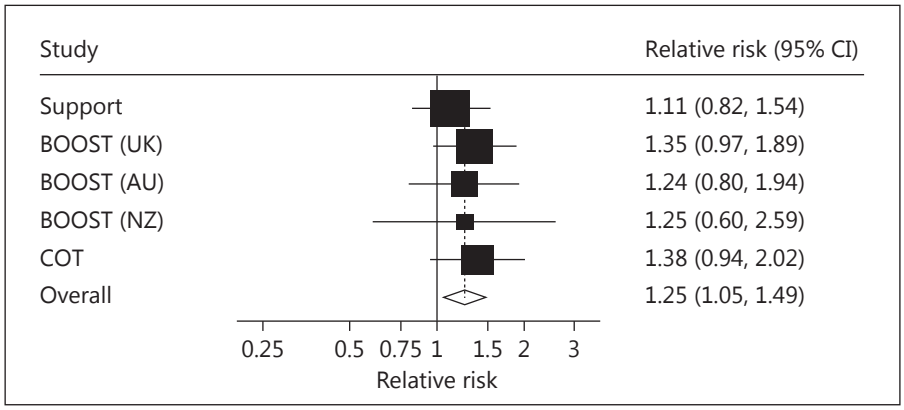

Fig. 3. Summary meta-analysis of NEC in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target.

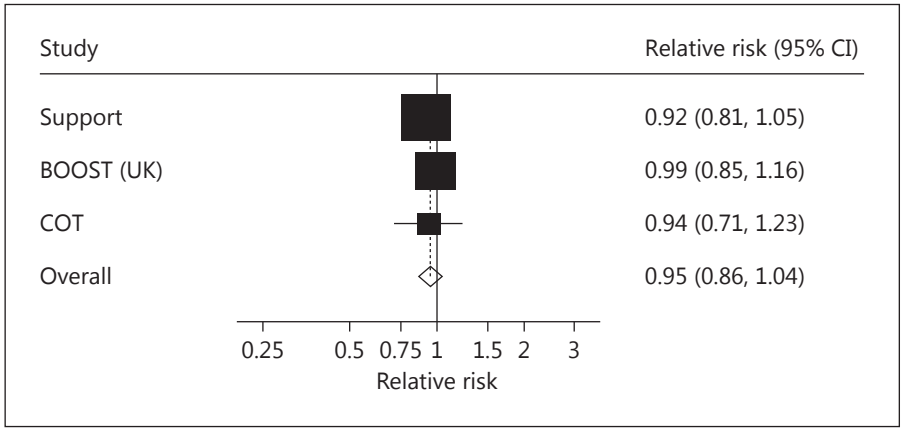

Fig. 4. Summary meta-analysis of BPD in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors high oxygen saturation target.

group versus 14.5% in the high saturation group, summary RR 0.74 (0.59–0.92), I^2 = 35%, $p_{heterogeneity}$ = 0.19; figure 2 shows data from the five individual studies.

NEC was recorded in the SUPPORT trial in 11.9% in the low and 10.8% in the high saturation group, RR 1.11 (0.82–1.51). In the 3 BOOST II trials, NEC was found in 10.4 versus 8.0%, RR 1.31 (1.02–1.68), and in the COT trial, it was diagnosed in 12.3% in the low and 9.3% in the high saturation group, RR 1.38 (0.94–2.02).

In all of the 5 trials a total of 11.2% in the low and 9.0% in the high saturation group developed NEC according to the different definitions applied, summary RR = 1.25 (1.05–1.49), I^2 = 0%, $p_{heterogeneity}$ = 0.70 (fig. 3).

Physiologic BPD in the SUPPORT trial was diagnosed in 38.0 and 41.7% in the low and high oxygen saturation groups, respectively, RR 0.92 (0.81–1.05). In the BOOST II (UK data only) trial, BPD was detected in 45.3 versus 45.7% in the low and high saturation groups, RR 0.99 (0.85–1.16). In the COT trial, BPD was diagnosed in 31.8 versus 33.1% in the low and high saturation groups, RR 0.94 (0.71–1.23). In total, 37.6% in the low and 39.7% in the high saturation group developed physiologic BPD at 36 weeks, summary RR = 0.95 (0.86–1.04), I^2 = 0%, $p_{heterogeneity}$ = 0.78 (fig. 4). Oxygen dependency at 36 weeks was found in 37.6 and 46.7% in the SUPPORT study, RR 0.82 (0.72–0.93), and 39.5 and 44.7% in the BOOST II studies, RR 0.90 (0.81–0.99). For all trials combined, the summary RR was 0.86 (0.77–0.96, I^2 = 45%, $p_{heterogeneity}$ = 0.14) (online suppl. fig. 3).

IVH ≥2 was detected in the SUPPORT study in 13.2 versus 12.7% in the low and high saturation groups, RR 1.06 (0.80–1.40). In the BOOST II trial, the numbers were 11.6 versus 10.4%, RR 1.12 (0.89–1.41). 'Brain injury' was detected in the COT trial in 20.6% in the low and 23.1% in the high saturation group, RR 0.85 (0.64–1.13). When combining all 5 trials applying these different outcomes

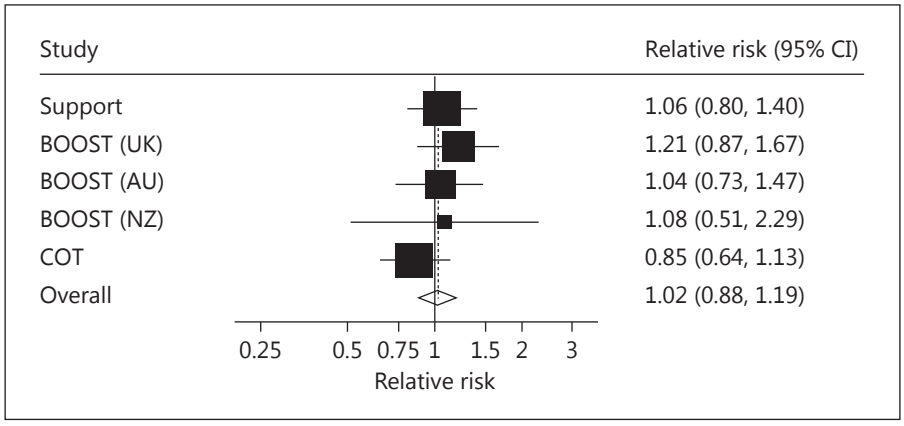

Fig. 5. Summary meta-analysis of IVH grade 2–4 brain injury in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target.

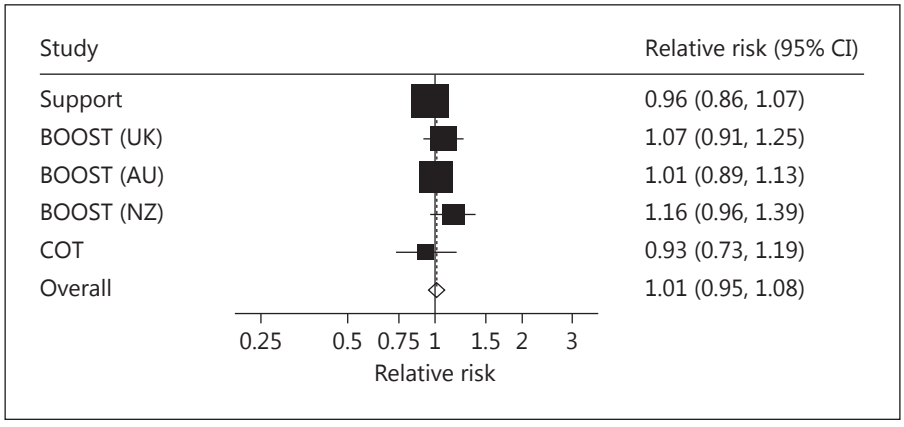

Fig. 6. Summary meta-analysis of patent ductus arteriosus in infants in low vs. high oxygen saturation target. RRs and 95% CIs are given. RR exceeding 1 favors a high oxygen saturation target.

as a marker of brain injury, 14.2% in the low and 14.1% in the high saturation group were positive, summary RR = 1.02 (0.88–1.19), $I^2 = 0\%$, $p_{heterogeneity} = 0.60$ (fig. 5).

For all 5 trials, patent ductus arteriosus was diagnosed in 49.2 and 49.0% in the low and high saturation groups, respectively, summary RR = 1.01 (0.95–1.08), $I^2 = 0\%$, $p_{heterogeneity} = 0.42$ (fig. 6).

Discussion

These 5 large studies aiming to clarify the optimal SpO_2 target postnatally in infants <28 weeks' gestational age have shown that mortality and NEC are significantly increased and severe ROP significantly decreased if SpO_2 is targeted low (85–89%) as compared with high (91–95%). However, there were no significant differences in the primary outcome (death or major disability) between the low and high oxygen saturation target groups of the 2 studies published so far. By applying the revised software, there was in COT a 6% increase in death or disability in the low compared to the high saturation group. The follow-up data of the BOOST II trials are therefore of great interest. The SUPPORT and the 3 BOOST II studies found a higher mortality in the low saturation group. The COT study did not demonstrate such a significant difference; however, there was a trend in the same direction. When combining all the data obtained with the revised algorithm there was a significant 40% increased mortality in the low versus the high saturation group. When all data including revised and nonrevised data are combined, an 18% increased risk of mortality in the low saturation target group was found. The SUPPORT data suggest one additional death for every 2 cases of severe ROP that are prevented by targeting the saturation in the low range.

Both the SUPPORT and BOOST II trials found less severe ROP in the low compared with the high saturation group; however, this was not confirmed by the COT trial. The combined results show a significant 26% reduction in severe ROP in the low compared with the high saturation group. Regarding NEC, there was a significant 25% increased incidence in the low saturation groups.

For BPD defined as oxygen requirement at 36 weeks' postmenstrual age noted in the BOOST UK and SUPPORT trials, there was a reduction in the low saturation groups. For obvious reasons, it was expected that more infants in the high saturation group would need oxygen supplementation. More importantly, therefore, are the results when applying the physiologic definition of BPD, and no significant reduction in the low compared with the high saturation group was found.

Neither 'brain injury' nor patent ductus arteriosus were significantly different between the groups.

Some differences in outcome between the trials were found. Are the differences in outcome between the trials due to different designs, patient characteristics, or in patient care? In the SUPPORT study, only 1 in 3–4 eligible infants were enrolled. Further, as mentioned above, the SUPPORT study included subjects before 2 h in contrast to the BOOST II and COT trials in which inclusion was performed within 24 h. The SUPPORT study included infants between 24 and up to 28 weeks of age, while the BOOST II and COT trials included infants <28 weeks of age. There are also differences in blinding procedures between the trials. Pooled effects from meta-analyses including randomized studies that were stopped (truncated RCT) early because of positive events are, however, likely to overestimate the effect, especially when there is a substantial difference in effect estimates between the truncated RCTs and the nonstopped RCTs, and in which the truncated RCTs have a substantial weight in the meta-analysis despite having a relatively small number of events [37].

Why were there significantly more deaths in the low saturation groups? This is another difficult question which needs an answer. In the trials, the major causes of death did not differ significantly between the two groups. However, Di Fiore et al. [38] recently demonstrated after analyzing the SUPPORT data that a low oxygen saturation target was associated with an increased rate of intermittent hypoxemic events. Interestingly, these findings were not only applied to the early postnatal period but also up to 57 days of life in which period the severity of the hypoxemic events even increased. The BOOST II trials found an increasing difference of deaths between the low and high saturation groups up to 70 days after birth. It might therefore be that a low saturation target early in life may trigger some long-term effects that predispose for death in vulnerable children even at a later time point.

Based on these studies, the most recent European guidelines recommend targeting functional SpO_2 between 90 and 95% [39]. This target range requires a very tight control with the upper limit.

There are still several additional unanswered questions in this field. We do not have data regarding infants with gestational age 28 weeks or more. Further, we do not know whether oxygen saturation should be constant throughout the whole postnatal period or should be increased at a certain stage [40]. Should SpO_2 targets be different for different gestational ages and are there subgroups of babies who need different targets as for instance growth retarded or if the infant is infected? To date, we do not have any evidence-based data that may help us answering these fundamental questions. Ideally, they should be answered by large randomized trials. However, it does not seem likely that such trials will be launched in the nearest future.

In conclusion, in babies <28 weeks' gestational age low saturation targets (85–89%) until 36 weeks postmenstrual age are associated with more deaths and more NEC, higher saturation targets (91–95%) are associated with more ROP. Until more studies have been performed, it is suggested to target SpO_2 in these babies at between 90 and 95%.

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