# The Netherlands retinopathy of prematurity study

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# Summary

Despite intensive research retinopathy of prematurity (ROP) is still an important cause of visual impairment or blindness in prematurely born infants. The number of infants susceptible for severe ROP continues to rise as the gestational age of infants continues to decrease due to improvements in perinatal care.

It is well established that early detection and timely treatment of ROP diminishes the chance of developing a permanent visual disability. An evidence-based screening guideline is an important tool to improve early detection. However, screening guidelines cannot be applied universally, as level of care and risk factors differ per nation. The aim of this thesis was to develop a new screening guideline for the Netherlands. To minimize the likelihood that an infant with severe ROP would be missed, this guideline required easy and widespread implementation and a high predictive value..

Before any new guideline can be developed, it is vital to assess current, nationwide practices regarding neonatal care, ROP screening and treatment. We performed a national, prospective observational study on incidence of ROP, risk factors, ROP screening coherence, influence of transfers between hospitals, treatment criteria and practices: the NEDROP study.

First we investigated the incidence of infants with a visual disability due to ROP that were registered in the Institutes for the visually impaired in the Netherlands. Chapter 2 describes a follow up study of three earlier Dutch studies and presents a 30 year overview of visual impairment due to ROP in the Netherlands. In addition to the incidence of visual impairment (VI) caused by ROP, concomitant disabilities in preterm neonates born between 2000 and 2009 were evaluated using data obtained from the Dutch Institutes for the visually impaired. In the study group of 42 infants with ROP (or visual impairment), we observed a gradual decrease of gestational age (GA) and birth weight (BW), an increase of duration of artificial ventilation (AV), supplemental oxygen administration, bronchopulmonary dysplasia (BPD), developmental delay, and behavioral abnormalities. Compared with the previous study (1994-2000), significantly fewer children were visually impaired due to ROP and the incidence of complete blindness significantly decreased. Although more children received treatment, one third did not. The incidence of concomitant disabilities remained remained unchanged (73.8 vs 68.6%).

Screening logistics and ophthalmological data of the NEDROP study are presented in Chapter 3. Participation in the NEDROP study was high: all screening ophthalmologists, neonatologists, and pediatricians of the neonatal intensive care units (NICU's) and high care centers (HC's) and one third of pediatricians of regional centers participated. All infants born with a GA <30 weeks and 85%-90% of infants with GA 30-32 weeks are admitted to a NICU. Therefore, our study provided good insight into screening logistics and incidence of ROP in the Netherlands. In total, 2033 infants were reported of which 1688 (83%) were screened. ROP developed in 324 infants (19.2%), with a low incidence of severe ROP (30 infants (1.8%)) of which only 17 infants (1%) were treated. Difficulties with

retrospective classification of infants in type 1 and 2 ROP suggested that ETROP criteria for treatment were not universally implemented at the time of the NEDROP study. The median post menstrual age (PMA) when ROP was first detected was 34.1 weeks. In 641 cases (38%), the initial screening examination was not performed within the required 42 days. In 99.2% of all cases, the date for follow up was accomplished within 3 days of the planned date. Transfer to another hospital increased the chance of not being screened from 12.9% to 25% in case of three transfers.

The reported data by neonatologists and pediatricians (GA, BW, date of birth, zip code and numbered multiple births), enabled coupling of our NEDROP database to the already existing perinatal registry. Yearly, more than 95% of infants born <32 weeks' gestation are reported to the Netherlands Perinatal Registry. Of the 1561 infants with GA <32 weeks and/or BW <1500 g reported in the NEDROP study, 1380 could be linked (88%) to the perinatal registry. Based on these data, a risk factor analysis was performed (Chapter 4). Similar to previous studies, a lower incidence of ROP was observed in females and after prenatal administration of glucocorticoids. We also confirmed previously reported risk factors including GA, BW, length of stay at a NICU > 28 days and Artificial Ventilation (AV) > 7 days. In addition, we found that treatment with inhaled nitric oxide (iNO) presented a risk factor for ROP development. Inhaled NO is commonly administered to the most severely ill neonates, and is a relatively new rescue therapy.

We then developed a new guideline with the aim to reduce the number of infants that require screening (Chapter 5), since screening is stressful to the neonate and time-consuming for the care-giver. Screening criteria were developed to assure that no infants with severe ROP were missed: GA <30 weeks and/or BW <1250g and a selection of infants with GA 30-32 weeks and/or BW 1250-1500g, with at least one of the following risk factors: AV, sepsis, necrotizing enterocolitis (NEC), postnatal glucocorticoids or use of cardiotonics. Applying these new criteria to our study group resulted in a 29% reduction in screening, at the cost of not detecting 4.8% infants with mild ROP but without missing any infants with severe ROP. This reduced the number of fundoscopies by 21%.

The final analysis conducted with the NEDROP data represents a cost-effectiveness study (Chapter 6). With increasing awareness for costs in health care, the aim was set to compare the effects and costs of the Dutch screening strategy with other risk factor guided screening strategies, including also strategies in which not all infants with severe ROP are detected. It proved possible to improve the cost effectiveness of the current Dutch guideline by screening infants with GA <30 weeks *and* BW <1250 g, and infants with GA 30-32 weeks and/or BW 1250-1500 g with one of the previously described risk factors. This screening strategy reduced the number of infants to be screened by 27%. Compared to the previous Dutch guideline dating from 1997, the current guideline has reduced yearly costs by €77,500. However additional yearly savings of €67,900 might be obtained by even more stringent screening strategy as shown in this study.

Even lower costs would be achieved by leaving out the requirement of not missing out on infants with severe ROP. However, this will increase the chance of missing infants with severe ROP and may therefore reduce the number of infants with improved visual acuity. As this poses ethical questions and infants with improved vision have a higher chance of getting a paid job and live independently, a safety approach was chosen when the criteria for the current Dutch guideline were set.

In Chapter 7, a special subgroup at risk for severe ROP is highlighted. Donors with twin-twin transfusion syndrome (TTTS) developed severe ROP, in contrast with the receiver twin who does not develop ROP at all. A large number of blood transfusions convene a possible deleterious effect by simultaneous suppletion of IGF-1 administered via these blood transfusions. Although their peripheral retina may be largely vascularized, they can develop potentially blinding ROP in a rapid and progressive way and should therefore be monitored closely, so treatment can be performed in time, and blindness can be prevented.