The Netherlands retinopathy of prematurity study

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Chapter 3

Outcome and quality of screening in a nationwide survey on retinopathy of prematurity in the Netherlands

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ABSTRACT

Purpose

Provide insight in natural history, screening and treatment policy of Retinopathy of Prematurity (ROP) in the Netherlands.

Methods

A multicenter, prospective, population based study (NEDROP) included all preterm infants born in 2009 in the Netherlands fulfilling the inclusion criteria for ROP-screening. Anonymized data from ophthalmologists, neonatologists and pediatricians were merged on identification number.

Results

Of 2033 reported infants, 1688 (83%) were screened for ROP. ROP stage was reported in 100%, zone in 94.4% and plus disease in 83%. ROP developed in 324 (19.2%), mild ROP (stage 1-2) in 294 (17.4%), severe ROP (stage 3 or more) in 30 (1.8%) and 17 (1%) were treated. The initial screening examination was not performed within the required 42 days in 641 (38%). Date for follow up was recorded 1973 times and accomplished within 3 days from the planned date in 1957 (99.2%). The chance of not being screened increased from 12.9% without transfer to another hospital to 23.5, 18.5 and 25% after respectively 1, 2 or 3 transfers.

Conclusion

The incidence of severe ROP and infants treated was low. NEDROP emphasizes that timing of initial examination and transfer to another hospital are issues of concern within the screening process.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vision threatening disease in prematurely born infants. Over the years, our knowledge about the disease has improved and its management is evolving. At the same time, advances in neonatal care result in survival of an increasing number of infants with an extremely low gestational age (GA) which are the most susceptible to develop severe ROP.[1] Careful screening and timely treatment play a key role in the reduction of the number of infants left with a permanent visual disability. Several countries have developed evidence-based guidelines for screening and treatment of ROP.[2–6] The last ROP guideline in the Netherlands, based on a national retrospective study by Schalij–Delfos et al[7], is dated from 1997. Additionally, the International Classification for ROP (ICROP) was revised in 2005, and the Early Treatment for ROP (ETROP) study changed the treatment algorithm.[8,9] Therefore, revision of the Dutch guideline was imperative. A 30-year overview on visual impairment due to ROP in the Netherlands showed an increased risk of ROP among infants with decreasing GA and birth weight (BW), a relative reduction of visual impairment due to ROP but also an indication that not all infants at risk might have been seen or treated in time.[10] So, before releasing a new ROP guideline, the necessity for insight in incidence and risk factors for ROP, adherence to the screening protocol and treatment policy in our country, called for a nationwide inventory on ROP: the NEDROP study.

METHODS

The NEDROP study is a multicentre, prospective, population-based study, and includes all preterm infants born in 2009 in the Netherlands that fulfilled the inclusion criteria for ROP-screening according to the prevailing guideline: GA <32 weeks and/or BW <1500 g, and preterm infants that needed ≥40% supplemental oxygen for more than 3 days. Neonatologists and paediatricians provided coded information on all those who were eligible to enrol in the study: initials (first letter of first name and surname), zip code, date of birth, GA and BW. Multiple births were numbered consecutively (1/2, 2/2, 1/3, etc). Ophthalmologists reported the same coded information of all infants that were actually screened for ROP. On a specially designed form, they reported the date of first examination, the suggested and executed dates of follow-up examinations, the date and reason for discontinuation of screening, ROP classification, presence or absence of plus disease and need for treatment. According to the prevailing guideline, the first screening examination should be scheduled at 5 weeks (before 42 days) postnatal age (PNA). For study purposes, infants were categorised as mild (ROP stages 1 and 2) or severe (ROP stage ≥3) ROP. However, some data will be presented by stage of ROP. In

retrospect, infants were classified in Type 1 and Type 2 ROP, according to the ETROP criteria. At transfer, the next hospital's name was noted. Data input for the NEDROP database was centralised and handled by one investigator (AvS).

Statistical analysis

Data files on patient characteristics and screening were merged on identification number. Numerical values are presented as medians with 25–75% IQR in brackets. Data about screening examinations and transfers are presented with minimum-maximum range. Data management and statistical calculations were done with the SAS V.9.2 package (SAS Institute, Cary, North Carolina, USA).

RESULTS

Population

All 103 hospitals involved in ROP screening (10 neonatal intensive care units (NICU), 16 high-care centres (HC) and 77 regional centres (RC)) participated in the study. Neonatologists and paediatricians reported 2033 infants eligible for screening of which 556 were part of twins or triplets. Infants were born at a NICU (1735; 85.3%), a HC (177; 8.7%) or a RC (121; 6%). Of the reported infants, 1688 (83%) were screened for ROP (figure 1). Their median BW and GA are presented in table 1. Of the reported infants, 164 died, of which four were fully screened and, therefore, included in the study. For several other reasons, infants were not screened or lost to follow-up: the ophthalmolo-

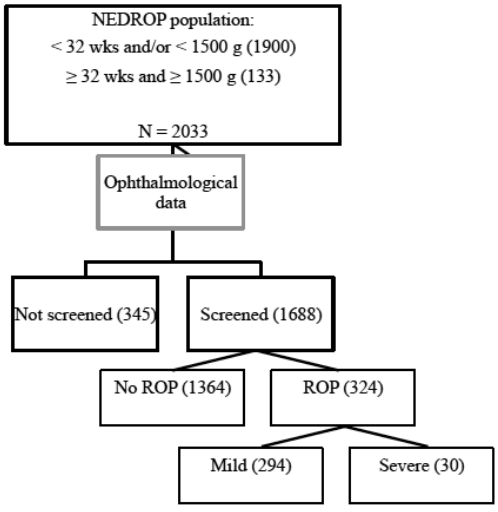


Figure 1 Flowchart

Table 1 Study population characteristics

	Screened for ROP	No ROP	Overall ROP	Mild ROP	Severe ROP
Patients (N)	1688	1364	324	294	30
GA	30.1 (28.6-31.4)	30.7 (29.3-31.7)	28.0 (26.4-29.4)	28.1 (26.6-29.6)	26.3 (25.4-27.0)
BW	1320 (1050-1560)	1400 (1150-1620)	950 (780-1212)	960 (790-1225)	890 (730-1060)
Examinations (N)	3891	2402	1489	1250	239
median	2 (1-3)	1 (1-2)	4 (3-6)	4 (3-6)	6 (5-10)
1st exam PMA	35.4 (33.7-37.0)	35.9 (34.4-37.1)	33.1 (31.4-34.9)	33.4 (31.6-34.9)	31.7 (31.0-34.1)
1st exam PNA	5.6 (5.0-6.4)	5.6 (5.0-6.4)	5.4 (5.0-6.1)	5.4 (5.0-6.1)	5.7 (5.1-6.7)
1st exam >42 days (N)	592	513	79	74	5
1st detection ROP PMA	NA	NA	34.1 (32.4-36.0)	34.3 (32.4-36.0)	34.0 (32.3-35.6)
1st detection ROP PNA	NA	NA	6.3 (5.3-7.7)	6.3 (5.3-7.6)	7.3 (6.0-8.0)

Number (N) of infants, screening examinations and initial examinations > 42 days after birth.
Median values with 25-75 IQR for gestational age (GA), birth weight (BW), number of examinations, 1st screening examination and first detection of ROP.
PMA = postmenstrual age, PNA = post natal age, NA = not applicable, exam = examination

gist was not summoned (126), different inclusion criteria for screening were used (23), transfer of the infant to another hospital before the first screening (12), no show at the outpatient appointment (10), and transfer abroad (4). For 10 infants, the reason was unknown. Due to the anonymous data retrieval, it is not known if those not screened developed ROP.

ROP

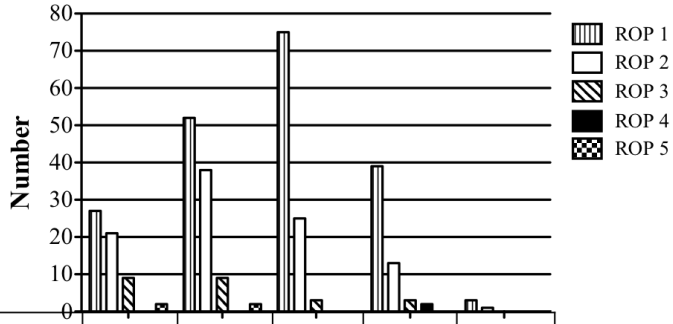
Of the 1688 infants screened, 324 (19.2%) developed ROP, of which 294 were mild and 30 severe (tables 1 and 2). The absolute numbers of infants with ROP increase with decreasing GA (figure 2). At time of detection, ROP was located in Zone I in 7, Zone II in 133 and Zone III in 166 cases. The zone was not noted in 18 (5.6%) infants. Plus disease was present in 32, absent in 237 and not noted in 55 (17%) infants. Treatment was performed in 17/324 infants with ROP (5.2%): three with ROP stage 2, 12 with ROP stage 3 and 2 with ROP stage 4.

In retrospect, infants were divided in Type 1 and Type 2 ROP, according to ETROP criteria: of the 324 infants 21 could be classified as Type 1 ROP, 10 as Type 2 ROP, 280 did not fit the criteria, and 13 could not be categorized due to incompleteness of data. Of the 21 infants with Type 1 ROP, 11 were treated (9× ROP 3, 2× ROP 2) and 10 regressed sponta-

Table 2 Characteristics of infants with ROP specified per stage

	N	GA	BW	Examinations (N)
ROP 1	196	28.4 (23 6/7-33)	1030 (440-2040)	3 (1-9)
ROP 2	98	27.4 (24 2/7-34)	890 (530-1660)	6 (2-12)
ROP 3	24	26.4 (24 2/7-31 3/ 7)	913 (600-1880)	6 (3-23)
ROP 4	2	30.7 (30-31 3/7)	1223 (975-1470)	4 (1-6)
ROP 5	4	25.7 (25 3/7-26 2/7)	675 (520-806)	13 (10-20)

Median gestational age (GA), birth weight (BW) and number of screening examinations with minimum-maximum range in brackets.



Weeks	23-25	26-27	28-29	30-31	≥32
ROP1	27	52	75	39	3
ROP2	21	38	25	13	1
ROP3	9	9	3	3	0
ROP4	0	0	0	2	0
ROP5	2	2	0	0	0

Figure 2 Number of infants with retinopathy of prematurity (ROP) and their distribution of gestational age (GA)

neously. Six treated infants could not be categorized, two with stage 4 and four because notification of zone or plus disease lacked.

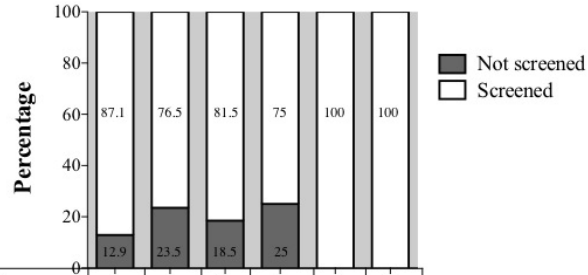
Screening

Ophthalmologists performed 3891 funduscopies. Infants that developed ROP were screened 1489 times, those without ROP2402 times. Roughly, the number of screening examinations increased with severity of disease (tables 1 and 2). Of the screened infants

544 (32.2%) had a BW ≥1500 g and 252 (14.9%) a GA ≥32 weeks. Data about initial screening and detection of ROP are displayed in table1. The initial screening was performed at a median age of 39 (11–334) days. At the first examination, 1480 had no ROP, 202 mild and six severe ROP. In 641 (38%) infants, the first screening examination was performed >42 days after birth. Three of these infants already had mild and five severe ROP. The date for follow-up screening was recorded 1973 times and accomplished within 3 days from the planned date in 1957 (99.2%). For five infants, the follow-up examination was outside this interval (range 1–8 weeks) without consequences for the outcome.

Transfer

More than half the population (59.6%) was born and cared for in the hospital of birth. The others were transferred once or more times, with a maximum of six (figure 3) times. Infants that had more than three transfers had been moved to and from a treatment centre. Of the non-transferred infants, 12.9% (156/ 1211), and of the infants with one or more transfers, 23% (189/822) had not been screened (p<0.001). However, no significant relation was found between the number of infants that were not screened, and the absolute number of transfers (p=0.64).



Transfers	0	1	2	3	4	6
Number of patients	1211	736	65	16	4	1
Screened	1055	563	53	12	4	1
Not screened	156	173	12	4	0	0

Figure 3 Number of transfers and percentage screened. Number of transfers and percentage of screened / not screened infants are presented in the graph. Absolute numbers are presented in the adjoining table.

DISCUSSION

This prospective, population-based study was conducted with participation of all centres involved in ROP screening, thus providing insight in natural history, screening and treat-

ment policy adherence in the Netherlands. This resulted in a large cohort of 2033 infants. The number of infants screened was high (83%) and comparable with a large cohort (n=13 282) described by Bain et al[11] who found an overall rate of missed ROP screening of 18.6% in 2005 and 12.8% in 2007. Comparison of results on incidence of ROP is complicated as most studies are retrospective and not nationwide, and inclusion criteria vary. There are a number of studies with inclusion criteria similar to ours. Hoogerwerf et al[12] studied a cohort retrospectively in the central part of the Netherlands, from 2001 to 2005. They found similar incidences for overall ROP (23.3%) and severe ROP (1.2%). Ho et al[13] found an incidence of 19.2% ROP (36/187), 9.6% severe ROP and 8.6% treatment in a retrospective study from 1996 to 2003 in a tertiary centre in the South Glasgow region. Larsson et al[5] performed a population-based study in Stockholm County, Sweden, from 1 August 1998 to 31 July 2000, and found ROP in 25.5% (100/392), severe ROP in 12.2% and treatment of 8.1%. Isaza et al[14] reported ROP in 40.4% (171/423), severe ROP in 9.2% and treatment in 5.7% in a retrospective study in a NICU in Canada from July 2006 to July 2010. A prospective study by Dhaliwal et al[15] performed in Lothian, Scotland, from 1990 to 2004 found ROP in 17%, severe ROP in 8.5% and 5% treatment in 474 infants born during 2000–2004.

The incidence of ROP in the current study (19.2%) is similar to most studies, but low for infants with severe ROP and those treated. The NEDROP population is large, covers the whole nation and includes all infants screened for ROP in 2009, also those ≥32 weeks and ≥1500 g (7.5%). This is reflected in a mean GA (30 weeks) and BW (1435 g) that is relatively high compared to the other studies, not including infants >32 weeks gestation. Only Isaza[14] also included those judged at risk.

Furthermore, only one NEDROP infant had a GA <24 weeks, probably due to the contemporary Dutch policy not to resuscitate infants at birth with a GA <24 weeks.

We found a low number of treated infants. Retrospectively, 21 infants were classified with Type I ROP of which 11 were actually treated. If all Type 1 ROP infants would have been treated (27/1688=1.6%), the difference with the studies above would still be substantial. In 17%, plus disease was not recorded. It is unknown if plus disease was not recorded because it was absent or whether the implication of plus disease was not appreciated by the ophthalmologist. An inventory on visual impairment due to ROP by van Sorge indicated that not all infants with severe ROP might have been treated in time.[10] This inventory again suggests that ETROP treatment criteria were not implied at large in 2009, and not all infants are treated in time. The old guideline did not include a section about treatment supporting the necessity for guidelines to include rules for screening and also for treatment. This has been effected in the new national ROP guideline.

This study provides useful information about the screening process. The main deviation of the protocol was a delay in the initial screening examination. According to the prevailing guideline, the first screening examination should take place at PNA 5 weeks

(<42 days). The median PNA at initial screening was 5.6 weeks. Figures about postmenstrual age (PMA) (median 35.4 weeks) are not well comparable with others due to the substantial number of infants with GA >32 weeks in this study. For unknown reasons, 641/1688 infants were screened >42 days of age. Eight of these infants already had ROP at the initial examination, of which five were severe. In a population-based study on severe ROP, Haines et al[16] also found that 31/221 (14%) infants already had severe ROP at first screening in contrast with 0.4% in our study. Gupta et al,[17] investigating 23 Canadian centers, found that eight different criteria were in use for timing of screening, and only 40% initiated screening at 4–6 weeks.

PMA and PNA for the development of ROP and severe ROP was similar to other studies.[18,19] A date for follow-up was recorded 1973 times and executed within 3 days of the intended date in 99%. This suggests that written recommendations increase the rate for follow-up.

Transfer has been reported as an important weak link in the screening process.[20] Reynolds et al[21] described 13 ROP malpractice cases of which eight were related to failure to refer or follow-up. Attar et al[20] found that the risk of not being screened at all was associated with transfer or discharge of the NICU before the initial eye examination, no written recommendation in the discharge summary, and no scheduled appointment at discharge to home.[22] We anticipated that transfer could be a bottle neck in our screening process as policy of transfer changed. In the past, at least the initial screening examination was performed in a NICU resulting in a careful selection of high-risk infants whose transfer was postponed. Currently, infants are transferred to a HC or RC as soon as they are respiratory and circulatory stable, often before the first screening examination. As lack of screening or delay in follow-up can have devastating consequences, we should direct our efforts towards optimisation of communication and distribution of information. A recent study by Barry et al[23] showed that the attendance rates for initial outpatient examinations and fulfilment of the screening programme significantly increased after they introduced parent education forms, streamlined scheduling and introduced a log book for follow-up monitored by the attending ophthalmologist. As a result of the NEDROP study, several indicators were added to our National Monitoring System for Quality in Health Care to improve the screening process. Shortly after births, parents should receive a ROP brochure, and the week for initial screening is defined and noted in the patient's medical record. The neonatologist is obliged to include information about ROP screening in the letter of transfer (including ophthalmological data and a week number for first or planned follow-up screening), or infants get a scheduled appointment before discharge to home. Although the anonimysed data admission facilitated participation of all centers involved, it was also a limitation as neonatal and ophthalmological data were available for each individual patient, but could not be linked directly to the centre of care. For example, for individual infants, we do not know the reason they were not

screened, or the reason for discontinuation of screening after transfer. Furthermore, this study covered only 1 year of screening. There is, however, no reason to assume that this year would deviate much from other years. Finally, we should consider variability in the judgment of different examiners for staging and treatment of ROP. As the group is large, this observer bias is expected to level out in the final results.

Gilbert et al[24] emphasized that each country should adjust its screening guidelines based on characteristics from its own population. The shortcomings in the execution of the 1997 guideline emphasize the need for evaluation of the implementation of guidelines even in well-structured healthcare systems. Ideally, this should be done in an obligatory national registry but the complexity to organize this as well as local privacy and legal regulations might prevent countries from institutionalizing such a register. The alternative is a national inventory on a regular basis. The NEDROP study resulted in a new guideline[25] for screening and treatment of ROP. Oral communication at regional and national meetings, quality indicators and an online e-learning should second all-encompassing implementation, the results of which will be evaluated in the next national inventory.

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Competing interests

None.

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