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Evaluation of new guidelines for ROP screening in Sweden using SWEDROP – a national quality register

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ABSTRACT.

Purpose: **To investigate whether recent Swedish guidelines for Retinopathy of Prematurity (ROP) screening, that is, a gestational age (GA) at birth of <31 weeks (w), are applicable in a new national cohort of prematurely born infants.**

Methods: **SWEDROP is a national register for ROP, initiated in 2006. The present paper reports on data from the register on various aspects of screening for ROP in infants born between 2010 and 2011 and compares the results with those for a previously published cohort born between 2008 and 2009.**

Results: **During the study period, 1744 infants were screened for ROP. Mean GA was 28.4 w (22–31), and mean birth weight was 1239 g (382–2615). Screening started at postnatal age (PNA) 5.4 w (0.4–13.3) and postmenstrual age (PMA) 33.8 w (24.9–50.1) Mean number of examinations was 5.4 per infant (1–38).Mild (stages 1–2) and severe (≥ stage 3) ROP was found in 15.4% and 8.7%, respectively. Treatment was performed in 4.2% (73/1744) of the infants, but in none with a GA of 30 weeks or more. The first treatment was performed at a mean PNA and PMA of 12.7 w (7.7–25.4) and 37.4 w (32.1–51.4), respectively.**

Conclusions: **Recently introduced new guidelines for ROP screening in Sweden remain applicable. Reassuringly, in infants born between 2010 and 2011, incidence of ROP, frequency and timing of treatment, frequency and timing of examinations and national coverage of ROP screening remained almost identical to those for a previous cohort from 2008 to 2009. The two SWEDROP cohorts provide a basis for discussion among Swedish ophthalmologists and neonatologists on the question of further lowering the upper screening limit with 1 week.**

Key words: guidelines – national register – retinopathy of prematurity – screening

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Introduction

Despite continuous improvements in neonatal care, retinopathy of prematurity (ROP) remains an important cause of childhood blindness worldwide (Gilbert 2007). Efficient screening for ROP to identify treatment-requiring disease and provide adequate treatment at the appropriate time is crucial. Guidelines for ROP screening differ in different countries and have to be adapted to the country in question. Furthermore, such guidelines have to be continuously evaluated and modified.

Swedish guidelines for ROP screening are based on population-based studies and have been continuously modified during the last 20 years. The first study recommended screening of all prematurely born infants born before a GA of 33 w (Holmström et al. 1993). Ten years later, the guidelines were changed, with screening recommended for infants with a GA of <32 w (Larsson & Holmström 2002). A few years ago, a national study of extremely preterm infants born before 27 w of age, the EXPRESS study, resulted in a recommendation to postpone the first examination until a postmenstrual age (PMA) of 31 w in these immature babies (Austeng et al. 2011). To further improve screening for ROP in Sweden, a national register, SWEDROP, was

initiated in 2006. Based on this register, analysis of data on ROP screening in Sweden for the period 2008 to 2009 resulted in new guidelines recommending screening of infants with a GA of <31 w (Holmström et al. 2012).

The aim of the present paper was to investigate whether the latter new guidelines, that is, inclusion criteria of a GA of <31 weeks and start of the first examination in the most immature babies in postmenstrual week 31, are still applicable in a new national cohort of prematurely born infants.

Methods

SWEDROP is a national quality register in which data on screening for ROP in all Swedish infants are registered. Only infants who are born and live in Sweden during the total period of ROP screening are registered in SWEDROP. Details regarding the register have been described previously in a report on infants born during the period 2008–2009 (Holmström et al. 2012). The present paper presents the results of infants born during the period 2010 to 2011 who were registered in SWEDROP. During that time, all infants with a GA of <32 w at birth were screened for ROP. The first examination was recommended to take place at a postnatal age of 5 w, but in the most immature infants (GA < 27 w), the first examination was postponed until a PMA of 31 w. Further examinations were performed at intervals of 1–2 weeks and were continued until the retina was fully vascularized. In infants with ROP, examinations continued until regression of the disease. Criteria for treatment followed the ETROP recommendations (Early Treatment for Retinopathy of Prematurity Cooperative Group 2003).

For the evaluation of national coverage of SWEDROP, comparison with a Swedish neonatal quality register (SNQ) was performed.

Statistical methods

Nonparametric methods for inferential statistics are used in all analyses for variables measured on an ordinal scale and for continuous variables because of skewness. Hence, the Spearman rank correlation coefficient was used to analyse relationships between severity of ROP, age (PMA and PNA) at onset of ROP stage 3, age at first treatment and GA and BW, respectively. The Mann–Whitney *U*-test was used when analysing differences in GA (w) and BW (g) in infants treated or not treated for ROP and when analysing differences in PMA at onset of ROP stage 3 in eyes later treated or not treated for ROP. The chi-square test was used to analyse differences between the frequency of treatment for ROP in boys and in girls.

The ethics committee of the Faculty of Medicine, Uppsala University, approved the study.

Results

During the study period from 1 Jan 2010 to 31 Dec 2011, 1757 infants with a GA of <32 w who were born and screened for ROP in Sweden were registered in SWEDROP.

Of these infants, 13 had died before termination of ROP screening, that is, before full vascularization or before full regression of any ROP. Three of the 13 dead infants had been treated for ROP (one with GA 23 w and two with GA 24 w).

Thus, the remaining study cohort comprised 1744 infants with a complete ROP screening.

During the study period, two infants (GA 27 and 30 w) were excluded from registration in SWEDROP. Both had herpetic keratitis which prevented proper ROP screening.

Another 78 infants with a GA of <32 w were registered in the Swedish neonatal quality register (SNQ), but were not screened for ROP nor registered in SWEDROP. The GA of 59 of these infants was 31 w, 16 infants had a GA of 30 w, and three infants had GAs of 29 w, 28 w and 27 w, respectively. Hence, there were a total of 1837 (1744 + 13 + 2 + 78) infants born during the study period with a GA of <32 w who should have been registered in SWEDROP, giving a dropout rate of 4.2% (78 of 1837 infants).

The total study cohort comprising 1744 infants had a mean GA at birth of 28.4 w (range 22–31) of whom 23.1% (403/1744) had a GA of 31 w. The mean BW was 1239 g (range 382–2615). There were 51.9% (906/1744) boys and 48.1% (838/1744) girls, and 72.2% (1259/1744) single and 27.8% (485/1744) multiple births.

Retinopathy of prematurity was found in 24% (419/1744) of the infants. Mild ROP (ROP stages 1 and 2) was found in 15.4% (268/1744), and severe ROP (ROP stages 3–5) was found in 8.7% (151/1744) of the infants, of whom two had ROP stage 4A, one ROP stage 4B and one ROP stage 5.

Finally, there were 64 infants who had been registered in SWEDROP, but not included in the study group, due to gestational ages above the upper limit for screening at that time, that is, above 31 (31 + 6) w of gestation. One of them had ROP stage 1 (GA 35 w), and two had ROP stage 2 (GAs of 32 w and 33 w, respectively.).

In the study cohort of 1744 infants, the severity of ROP was significantly correlated with both GA (w) at birth and BW (g) ($p < 0.001$, correlation coefficients – 0.575 GA/−0.560 BW). The distribution of the different stages in relation to GA is illustrated in Fig. 1. None of the infants with a GA of 31 w, one infant with a GA of 30 w and three infants with a GA of 29 w developed stage 3 ROP.

Treatment for ROP had been performed in 4.2% (73/1744) of the infants, of whom one had a GA of 29 w at birth, three had a GA of 28 w, and the remaining treated infants had GAs below 28 w, see Fig. 2. There was a significant association between treated ROP and GA (w) at birth and BW (g), respectively ($p < 0.001$), but there was no significant association ($p = 0.234$) with gender.

Screening

Number of examinations

A total of 9369 eye examinations had been performed during the study period. The mean number of eye exam-

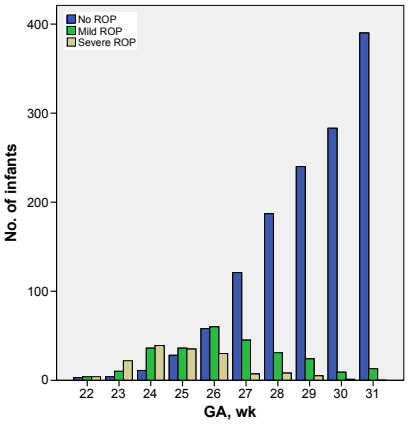

Fig. 1. Number of infants with no, mild (stages 1–2) and severe (≥ stage 3) Retinopathy of Prematurity (ROP) in relation to gestational age (GA), wk (week), at birth.

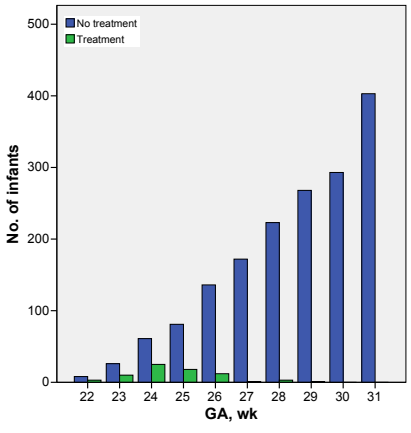

Fig. 2. Number of infants who have been treated for Retinopathy of Prematurity (ROP) in relation to gestational age (GA), wk (week), at birth.

inations was 5.38 per infant (range 1–38). The number of examinations was significantly correlated with GA(w) at birth ($p < 0.001$, correlation coefficient – 0.799). Infants born with a GA of 31 w had a mean of 2.4 examinations, as compared to 14.0 examinations in infants with a GA of 22–23 w. Altogether, infants with a GA at birth of 31 w had 970 examinations, that is, 10.4% (970/9369) of the examinations for the total cohort.

The mean postnatal age (PNA) at the first examination was 5.4 w (range 0.4–20.1, SD 1.34) in the total study group. In infants born at a GA of ≤26 w and >26 w, the mean PNA at the first examination was 6.3 w (range 1.9–12.1, SD 1.38) and 5.1 w (0.4–20.1, SD 1.21), respectively. In infants born at a GA of > 26 w, 86.7% (1182/1364) had been examined before a PNA of 6 w, 95.9% (1308/1364) before a PNA of 7 w and 97.9% (1336/1364) before a PNA of 8 w.

The mean postmenstrual age (PMA) at the first examination was 33.8 w (range 24.9–50.1, SD 2.166). In infants born at a GA of ≤26 w and >26 w, the mean PMA at the first examination was 31.2 w (range 24.9–37.7, SD 1.41) and 34.5 w (28.5–50.1, SD 1.79), respectively. In infants born at a GA of ≤26 w, 93.7% (356/380) were examined before a PMA of 33 w and 97.1% (369/380) before a PMA of 34 w.

Onset of ROP stage 3 and age at first treatment for ROP

The mean (range) PNA and PMA at onset of ROP stage 3 in at least one of the eyes of the infants were 11.8 w (5.1–27.6) and 36.7 w (31.1–52.6), respectively.

The PMA (w) at onset of ROP stage 3 was significantly associated with GA at birth (w), that is, the lower the GA at birth, the lower the PMA at onset of ROP stage 3 ($p < 0.001$, correlation coefficient 0.410). There was no significant correlation between PNA at onset of ROP stage 3 and GA at birth ($p = 0.239$).

The first treatment was performed at a mean (range) PNA of 12.7 w (7.7–25.4) and a mean (range) PMA of 37.4 w (32.1–51.4). There was a significant correlation between PMA at first treatment and GA at birth ($p = 0.001$, correlation coefficient 0.413), but not between PNA at first treatment and GA at birth ($p = 0.672$).

The mean PMA at onset of ROP stage 3 was lower in eyes treated for ROP (35.8 w) than in eyes that did not progress to a stage where treatment was required (37.6 w) ($p = 0.004$).

Discussion

With the help of SWEDROP, a national register for ROP, analysis of a new cohort of infants born between 2010 and 2011 revealed that recently introduced new guidelines for ROP screening in Sweden remain applicable. No infant who had been treated for ROP had a GA of more than 29 w. None of the 64 infants who had been referred for screening despite a GA above 31 w, possibly because of general illness, developed more than ROP stage 2. Hence, the recently introduced recommendation for an upper screening limit of <31 w still applies (Holmström et al. 2012). Furthermore, no infant had an onset of ROP stage 3 before 31 w PMA and no infant was treated before a PMA of 32 w, regardless of GA at birth. Consequently, the recommended start for screening for ROP at 31 w in the most immature babies remains relevant (Austeng et al. 2011).

Comparison of data for the two cohorts, born 2010 to 2011 and 2008 to 2009, revealed that the populations were almost identical regarding GA at birth (28.4 w for both cohorts) and BW (earlier cohort 1242 g/present cohort 1239 g) (Holmström et al. 2012). Further, the incidences of ROP and the different stages of ROP, the time at onset of ROP stage 3 and the timing of treatment, were all very similar in the two cohorts, see Tables 1 and 2. In the present study, the most immature infants had an earlier onset of ROP stage 3 and were treated at an earlier PMA than the less immature infants. Hence, the previous recommendation to focus on the most immature infants and on those with an early onset of severe ROP still applies (Austeng et al. 2011).

The national coverage of ROP screening in Sweden was similar in the two cohorts from 2008 to 2009 (96%) and

Table 1. Stage of ROP and Treatment for Retinopathy of Prematurity (ROP) in two Swedish cohorts, 2008–2009* and 2010–2011, respectively.

	No of infants	No ROP *n* (%)	ROP 1 *n* (%)	ROP 2 *n* (%)	ROP 3 *n* (%)	ROP 4 *n* (%)	ROP 5 *n* (%)	Treatment *n* (%)
2008–2009	1789	1354 (75.9%)	119 (6.7%)	159 (8.9%)	146 (8.2%)	4 (0.2%)	2 (0.1%)	78 (4.4%)
2010–2011	1744	1325 (76%)	124 (7.1%)	144 (8.3%)	147 (8.4%)	3 (0.2%)	1 (0.1%)	73 (4.2%)

*Ref Arch Ophth 2012.

Table 2. Time at Onset of Retinopathy of Prematurity (ROP) stage 3 and at first Treatment in two Swedish cohorts, 2008–2009* and 2010–2011, respectively.

	PNA at Onset ROP stage 3	PMA at Onset ROP stage 3	PNA at first Treatment	PMA at first Treatment
2008–2009	11.4 (5.7–19.9)	36.6 (31.1–45.9)	12.6 (7.3–20.6)	37.0 (32.3–46.6)
2010–2011	11.8 (5.1–27.6)	36.7 (31.1–52.6)	12.7 (7.7–25.4)	37.4 (32.1–51.4)

*Ref Arch Ophth 2012.

2010 to 2011 (95.8%) (Holmström et al. 2012). Despite the rather high coverage, further improvements are desirable. A better communication with neonatologists is important, as four per cent of the infants with a GA <32 w had not been referred for ROP screening. Furthermore, SWEDROP is continuously modified and improved, and a recent possibility to import data on every newborn infant from the Swedish neonatal quality register, SNQ, on a weekly basis, might enable detection of infants who are not referred for ROP screening. Hopefully, this technical improvement may further increase the national coverage.

The frequency of examinations was almost identical in the two Swedish cohorts of prematurely born infants from 2008 to 2009 (mean number of examinations 5.2) and 2010 to 2011 (mean number of examinations 5.4) (Holmström et al. 2012). The start of screening, however, is still too late. Timing of the first examination in the two cohorts is not comparable, as a new recommendation to postpone the first examination to a PMA of 31 w in infants born at ≤26 weeks had been introduced in the second study period. Although 86.7% of the infants born at a GA of >26 w in the present study cohort had been examined at an appropriate time, at a PNA of 5 w, there is still potential for improvement. This also applies to infants born at a GA of ≤26 w, of whom 6.3% had their first examination after a PMA of 32 w, that is, the earliest PMA for treatment.

In summary, the two Swedish cohorts of preterm infants born 2008–2009 (Holmström et al. 2012) and 2010–2011 are very similar and provide a robust basis for discussion on various aspects of screening for ROP. Such screening fulfils the principles defined by WHO (Wilson & Junger 1968). However, repeated eye examinations in these immature babies are costly and also stressful for the babies. Reduction of infants screened for ROP is therefore desirable. As previously mentioned, the upper limit of screening was recently lowered from <32 to <31 weeks of gestation at birth (Holmström et al. 2012), which would have reduced the number of infants screened with 24% and the examinations by 10%. A further lowering to less than 30 weeks would have reduced the number of screened infants in the present cohort with 293 and the number of performed examinations with 908, that is, with around another 10% reduction.

Although the purpose of screening guidelines is to identify and treat Type 1 ROP at an appropriate time, there is always a risk of outliers, who will escape the screening program. Our goal is to minimize this risk, and therefore some kind of margin of safety is desirable. In the previous cohort, no infant with a GA of 29 or 30 w was treated for ROP (Holmström et al. 2012). In the present cohort, one twin girl with a GA of 29 w was treated twice for ROP 3, Type 1, in both eyes. No infant with a GA of 30 w, however, was treated, while one boy developed ROP 3, zone II, Type II, which regressed spontaneously without treatment. Hence, lowering the upper limit of the Swedish screening guidelines to <30 weeks could be a possibility. In the current guidelines, with an upper limit of <31 weeks, neonatologists are already recommended to refer also infants with higher gestational ages if they are severely ill with other comorbidities (Holmström et al. 2012)). If further lowering the upper screening limit to <30 weeks, an additional way to go forward might be to use an algorithm based on the Swedish population and taking growth into account (Wu et al. 2012) in infants with "border line" gestational ages at birth, such as gestational weeks 30 and 31.

Changing guidelines for ROP screening entails a big responsibility. A national quality register provides good basis for continuous evaluation of the screening, as well for decisions of modification of existing guidelines. The results of the two SWEDROP studies will be a basis for discussion among Swedish ophthalmologists and neonatologists on the delicate question of further lowering the upper screening limit with 1 week.

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References

Austeng D, Källen KB, Hellström A, Jakobsson PG, Johansson K, Tornqvist K, Wallin A & Holmström GE (2011): Screening for retinopathy of prematurity in infants born before 27 weeks' gestation in Sweden. Arch Ophthalmol **129**: 167–172.

Early Treatment for Retinopathy of Prematurity Cooperative Group (2003): Revised indications for the treatment of retinopathy of prematurity: results of the early treatment for retinopathy of prematurity randomized trial. Arch Ophthalmol **121**: 1684–1694.

Gilbert C (2007): Changing challenges in the control of blindness in children. Eye **21**: 1338–1343.

Holmström G, el Azazi M, Jacobson L & Lennerstrand G (1993): A population based, prospective study of the development of ROP in the Stockholm area of Sweden. Br J Ophthalmol **7**: 417–423.

Holmström GE, Hellström A, Jakobsson PG, Lundgren P, Tornqvist K & Wallin A (2012): Swedish National Register for Retinopathy of Prematurity (SWEDROP) and the Evaluation of Screening in Sweden. Arch Ophthalmol **130**: 1418–1424.

Larsson E & Holmström G (2002): Screening for ROP – evaluation and modification of guidelines. Br J Ophthalmol **86**: 1399–1402.

Wilson JMG & Junger G (1968): Principals and practice of screening for disease. Geneva: World Health Organization.

Wu C, Löfqvist C, Smith LEH, VanderVeen DK, Hellström A & for the WINROP Consortium (2012): Importance of early postnatal weight gain for normal retinal angiogenesis in very preterm infants - a multicenter study analysing weight velocity deviations for prediction of retinopathy of prematurity. Arch Ophthalmol **130**: 992–999.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. ROP screening doctors in Sweden.