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Low Incidence of Sight-Threatening Retinopathy of Prematurity in Infants Born Before 28 Weeks Gestation at a Neonatal Intensive Care Unit in Japan

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Improvement in neonatal care has led to increased survival rates of very premature infants. Accordingly, there are now more extremely preterm infants who are at risk of developing retinopathy of prematurity (ROP). ROP is a disorder of low birth-weight preterm infants and may lead to blindness. However, the prevalence of ROP varies globally, depending on different neonatal and ophthalmic care. Therefore, we studied the incidence and progression of ROP in extremely preterm infants in Japan. In addition, we investigated the characteristics and the clinical courses of the infants who progressed to sight-threatening ROP. A total of 3,154 infants were born at the Japanese Red Cross Sendai Hospital between 2009 and 2011, including 53 live-born infants born before 28 weeks' gestation. Two extremely preterm infants died before the first ROP examination. Among the survived 51 infants (the birth-weight ranged from 309 to 1,354 g, mean 779 g), 36 infants (70.6%) developed ROP: 18 infants with mild ROP and 18 infants with severe ROP. Eight out of the 51 infants (15.7%) underwent laser treatment. None of the infants born at older than 27 weeks 0 day of gestation required any treatment for ROP. In conclusion, most of extremely preterm infants develop some degree of ROP. However, in the majority of these infants the ROP never progressed beyond mild disease and resolved spontaneously without treatment. Sight-threatening ROP was rare. The present study clarifies the natural history of ROP in extremely preterm infants with active perinatal care.

Keywords: infant; oxygen saturation; preterm infants; pulse oximeter; retinopathy of prematurity
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Introduction

Retinopathy of prematurity (ROP) is a disorder that involves the developing retina in low birth-weight preterm infants and can potentially lead to blindness. The blood vessels of the retina begin to develop at 4 months after conception and complete their development by the time of full-term birth (Azar and Davis 1999). The development of the retina normally proceeds from the optic nerve head anteriorly during the course of gestation. However, in preterm infants, this development is incomplete. Thus, the extent of the immaturity of the retina depends mainly on the degree of the prematurity at birth. ROP was first noted in the late 1940s in preterm infants and described as retrolental fibroplasia (Terry 1942). At the present time, we now think this initial description may have represented stage 5 ROP, which is the most advanced stage of ROP and characterized by total retinal detachment. In the past, routine use of excess oxygen was used to treat premature infants, which stimulated abnormal vessel growth. A previous study has investigated the oxygen saturation range that is appropriate for minimizing ROP without increasing adverse outcomes (Tin 2004). Currently, ROP is believed to be the result of the unstableness of the retinal vascular development and can be triggered by several factors, including excessive or fluctuating oxygen levels (Chen and Smith 2007; Hartnett and Penn 2012).

Today, continuous improvements in neonatal care have led to increased survival rates of very premature infants and a new population of extremely preterm infants. As a result, there are now more extremely preterm infants who are at risk of developing ROP. However, the prevalence of ROP varies globally, depending on different neonatal and ophthalmic care. Moreover, the incidence and natural history of ROP in infants with younger gestational ages (GA) have not been investigated in depth, especially in Asian countries.

Therefore, the aim of this study was to evaluate the incidence and progression of ROP in extremely preterm infants born at the Japanese Red Cross Sendai Hospital from 2009 to 2011. In addition, baseline characteristics, comorbidities, and the features of the clinical courses of the

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infants who required surgical intervention were also investigated.

Methods

This study was approved by the institutional ethics committee, and the parents of the patients provided informed consent before the infants were enrolled.

There were 3,154 infants born at the Japanese Red Cross Sendai Hospital (Sendai, Japan) from 2009 to 2011. The present study enrolled a total of 51 extremely preterm infants born between 23 weeks 0 day and 27 weeks 6 days of gestation from all of the patients who were admitted to the Japanese Red Cross Sendai Hospital neonatal intensive care unit (NICU) between June 1, 2009 and October 31, 2011. All infants were inborn, with those known to have major congenital anomalies excluded from the study.

Oxygen saturation in all infants was maintained within a physiologic reduced target range. This physiologic reduced oxygen protocol (PROP) was implemented as a way to maintain the oxygen saturation values, which were determined by a pulse oximeter (SpO_2), between 85% and 93% within the first 2 hours after birth (Chow et al. 2003; Wright et al. 2006). PROP was continued until 36 weeks of postmenstrual age (PMA) or until the infant was breathing ambient air and did not require ventilator support or nasopharyngeal continuous positive airway pressure (CPAP) for more than 72 hours, whichever occurred first.

Ophthalmic examination began by 33 weeks of PMA and continued until regression of ROP was observed. All infants were followed by one ophthalmologist (H.A.), with the diagnosis confirmed by another experienced pediatric ophthalmologist (M.N.). Fundus examination was performed by using binocular indirect ophthalmoscopy with an eyelid speculum in place along with scleral depression. Classification of ROP was performed according to the International Classification of ROP (ICROP) revisited (Gole et al. 2005) (Table 1). Aggressive posterior ROP (AP-ROP) was defined as a severe form of ROP characterized by its posterior location, prominence of plus disease, the ill-defined nature of the retinopathy, and the rapid progression to stage 5 ROP (Gole et al. 2005). Treatment criteria were based on the Early Treatment for Retinopathy of Prematurity (ETROP) recommendation (Good et al. 2003, 2005) (Table 1).

The following data were also collected for each infant: GA at birth, birth-weight, weekly postnatal weight measurements, gender, ROP findings including the ROP stage, zone, clock hours of fibrovascular tissue, postmenstrual age at the

Table 1. Current management of retinopathy of prematurity.

Criteria for screening
United States (2013)[a]: infants with a gestational age of ≤ 30 weeks or birth-weight of ≤ 1,500 g and selected infants with a gestational age of > 30 weeks and an unstable clinical course
United Kingdom (2008)[b]: infants with a gestational age of < 32 weeks or birth-weight of < 1,501 g
Sweden (2012)[c]: infants with a gestational age of ≤ 30 weeks 6 days
Timing of screening and examinations
First examination at a chronological age of 4-9 weeks or postmenstrual age of 31 weeks
Repeated examinations recommended by the examining ophthalmologist on the basis of retinal findings and suggested schedule
Classification of retinopathy of prematurity according to ICROP revisited (2005)
Zone (area of retinal vascularization)
I: vascularization within a circle centered on the optic nerve head, the radius of which is twice the distance from the optic nerve to the macula
II: vascularization extending beyond zone I, within a circle the radius of which is the distance from the optic nerve to the nasal ora serrata
III: vascularization extending beyond zones I and II
Stage (disease severity)
1: line
2: ridge (with volume)
3: intravitreal angiogenesis
4: partial retinal detachment
5: total retinal detachment
Plus disease: dilatation and tortuosity of retinal vessels
Treatment
Application of laser to peripheral avascular retina for type 1 retinopathy of prematurity
Zone I: stage 3, or stage 1 or 2 with plus disease
Zone II: stage 2 or 3 with plus disease

[a], Fierson, et al. 2013 USA policy statement for retinopathy of prematurity screening examination;
[b], Fielder, et al. 2008 UK retinopathy of prematurity guideline www.rcpch.ac.uk/ROP;
[c], Holmström, et al. 2012 Swedish national register for retinopathy of prematurity (SWEDROP) and the evaluation of screening guideline; ICROP revisited, Gole, et al. 2005 the revised international classification of retinopathy of prematurity.

initial application of laser treatment, the presence of severe systemic complications (e.g., intraventricular hemorrhage (IVH) grade III or IV, bronchopulmonary dysplasia (BPD), symptomatic patent ductus arteriosus (PDA) requiring surgical ligation or indomethacin therapy, necrotizing enterocolitis (NEC) requiring surgery, and anemia requiring transfusions), and the duration of oxygen therapy including mechanical ventilation and CPAP.

Results

Background data of the present study are given in Table 2. A total of 3,154 infants were born at the Japanese Red Cross Sendai Hospital from 2009 to 2011, including 53 live-born infants born before 28 weeks' gestation. Seven infants died before termination of screening examinations, including 2 extremely preterm infants died before the first ROP examination. None of the infants had any major abnormalities. Of the 51 extremely preterm infants who survived and were examined in this study, the GA at birth ranged from 23 weeks 0 days to 27 weeks 6 days (mean, 26 weeks 1 day), while the birth weight ranged from 309 to 1,354 g (mean, 779 g). The study group consisted of 26 males (51%) and 25 females (49%), with 40 single births (78.4%), 5 twin births (9.8%), and 6 triplet births (11.8%) recorded.

Table 3 shows the incidence of ROP and treated ROP. A total of 36 out of the 51 (70.6%) infants developed ROP, with 8 of the 51 (15.7%) requiring laser treatment. The 8 treated infants consisted of 2 males (25%) and 6 females (75%) from 7 single births (87.5%) and 1 twin birth (12.5%). None of the infants born at older than 27 weeks 0 day of gestation required any treatment for ROP.

Table 4 shows the Classification of the Active Stage According to ETROP. The maximal ROP attained by the worst eye was assessed. Out of the 51 preterm infants, 15 (29.4%) exhibited no ROP, 18 (35.3%) had non-prethreshold ROP, 8 (15.7%) had type 2 ROP, and 10 (19.6%) had type 1 ROP, with 8 (15.7%) undergoing laser treatment. Zone I ROP or aggressive posterior ROP was not observed.

Table 5 shows the postnatal course and weight gain for the treated ROP infants, which included 2 males and 6 females. The mean GA was 25.2 weeks, and the mean birth weight was 626 g. Ophthalmic examination began between 32.1 and 33 weeks of PMA. The first proliferative changes were found between 34.1 and 38.2 weeks of PMA. The initial laser treatments were performed between 34.1 and 39.1 weeks of PMA. The ROP status was stable between 39.5 and 44.6 weeks of PMA. Infant no. 224 exhibited a poor weight gain and subsequently developed severe ROP, with cataract observed at a chronological age of 10 months.

Table 6 shows the clinical characteristics of the treated ROP infants. The extent of the fibrovascular tissue ranged from 4 to 12 clock hours. Laser treatments were performed within zone II in 7 infants. One other infant treated within the posterior zone II was determined to be of the wedge type at the time of the examination. Out of the 8 treated infants, 6 had a prominent anterior tunica vasculosa lentis, while 7 had a remnant of the hyaline artery. All infants had favorable structural outcomes.

Discussion

Better neonatal care has led to high rates of survival of

Table 2. Background data for infants born at the Japanese Red Cross Sendai Hospital from 2009 to 2011.

Data	Number of infants
Live-born infants, total	3,154
Present study of live-born infants (< 28 weeks)	53
Infants who died before the first ROP examination	2
Infants who died after the first ROP examination	0
Infants excluded because of Down syndrome	0
Present study of screened for ROP	51

ROP, retinopathy of prematurity.

Table 3. Incidence of ROP and treated ROP.

Gestational age at birth (weeks)	Number of infants	Incidence of ROP	Incidence of treated ROP
23	5	4/5 (80%)	1/5 (20%)
24	8	8/8 (100%)	2/8 (25%)
25	10	8/10 (80%)	2/10 (20%)
26	14	9/14 (64%)	3/14 (21%)
27	14	7/14 (50%)	0/14 (0%)
Total	51	36/51 (70.6%)	8/51 (15.7%)

ROP, retinopathy of prematurity.

Table 4. Classification of the active stage according to ETROP.

Gestational age at birth (weeks)	Total	No ROP	Non-PT ROP	Type 2 ROP	Type 1 ROP	Treated ROP
23	5	1	3	0	1	1
24	8	0	2	2	4	2
25	10	2	3	3	2	2
26	14	5	5	1	3	3
27	14	7	5	2	0	0
Total	51	15 (29.4%)	18 (35.3%)	8 (15.7%)	10 (19.6%)	8 (15.7%)

No ROP, immature vascularization; Non-PT ROP, zone II or III stage 1 ROP without plus disease; Type 2 ROP, zone II stage 3 ROP without plus disease; Type 1 ROP, zone II stage 3 ROP with plus disease; Treated ROP, high-risk prethreshold ROP or threshold ROP; ROP, retinopathy of prematurity; ETROP, early treatment for retinopathy of prematurity; PT, prethreshold.

Table 5. Postnatal weight gain of treated infants.

Patient number	Gender	Gestational age (weeks) Birth-weight (grams)	Age at initial examination PMA (weeks) BW (grams)	Age at initial proliferative ROP PMA (weeks) BW (grams)	Age at initial laser treatment PMA (weeks) BW (grams)	Age at stabilization of ROP PMA (weeks) BW (grams)
80	Female	23.3 498	32.1 785	34.1 900	34.6 927	39.6 1,547
91	Female	24.3 660	32.5 1,000	35.5 1,345	36.3 1,410	42.3 2,248
122	Male	26.6 974	32.6 1,229	38.1 1,889	39.1 2,110	42.0 2,579
24	Female	26.1 760	32.2 1,000	38.2 1,726	39.0 1,787	42.3 2,470
61	Male	25.1 766	32.5 1,105	34.1 1,305	34.1 1,305	40.3 2,198
66	Female	25.3 397	33.0 767	34.5 849	34.5 849	39.5 1,341
224	Female	24.0 486	33.0 847	36.6 990	37.1 996	44.6 1,860
125	Female	26.6 469	32.3 763	37.3 1,269	38.1 1,333	41.5 1,809

PMA, postmenstrual age (gestational age at birth plus chronological age); BW, body weight; ROP, retinopathy of prematurity.

very premature infants who would have had little chance of survival in the past. Therefore, it is of clinical significance to know the incidence of ROP in extremely preterm infants. The present study showed that the incidence of ROP was 70.6% (36/51) in infants born before 28 weeks' gestation. Out of the 51 preterm infants, 18 (35.3%) had mild ROP (stage 1-2), while 18 (35.3%) had severe ROP (stage 3), with 8 (15.7%) undergoing laser treatment. None of the infants progressed to stages 4 and 5 ROP. In the present study, we found that the incidence of the maximum stages of ROP coincided with the national population-based cohort study of infants born before 27 weeks' gestation in Sweden (Austeng et al. 2009) (Table 7).

Improvements in neonatal care, which include an increase in centralization and better provision of intensive care for extremely preterm infants, have been implemented over the last decade. Starting in 2008, the Japanese Red Cross Sendai Hospital began using PROP for extremely preterm infants. Similar to many previous studies (Sears et al. 2009; Ellsbury and Ursprung 2010), PROP has been found to significantly reduce the incidence of severe ROP without increasing adverse outcomes.

In a previous study performed in our NICU (Chiba et al. 2012), they also reported a striking decrease in severe ROP (stage 3, 4, 5, or surgical). During the time period, the mortality rate remained stable. Incidences of bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage and patent ductus arteriosus were not significantly different. From an ophthalmological point of view, none of our infants exhibited Zone I ROP or aggressive posterior ROP. In addition, all of the infants that required laser treatment had favorable structural outcomes. Moreover, none of the infants born at older than 27 weeks 0 day of gestation required any treatment for ROP.

Screening examination for ROP at the Japanese Red Cross Sendai Hospital normally begins between 32 and 33

Table 6. Postnatal characteristics of treated infants.

Patient number	Zone	Stage	Extent of FT (clock hours)	Apgar score at 5 min	PDA	BPD	IVH	NEC	Transfusions	Period of intubation and ventilation Chronological age, days; (PMA, weeks)	Period of n-CPAP Chronological age, days; (PMA, weeks)	End of oxygen application Chronological age, days; (PMA, weeks)
80	II	3	Right12 Left 12	9	Yes	Yes	No	No	Yes	0-51 (30)	51-84 (35)	99 (37)
91	II	3	Right10 Left 10	9	Yes	Yes	No	No	Yes	0-55 (32)	55-68 (34)	75 (35)
122	II	3	Right 4 Left 4	9	No	Yes	No	No	No	1-35 (31)	0-1, 35-77 (37)	114 (43)
24	II	3	Right 6 Left 5	7	Yes	Yes	No	No	No	0-51 (33)	51-68 (35)	95 (39)
61	II post.	3	Right 6 Left 6	6	Yes	Yes	No	No	Yes	0-48 (32)	48-75 (35)	81 (36)
66	II	3	Right10 Left 10	9	Yes	Yes	No	No	Yes	0-63 (34)	63-77 (36)	112 (41)
224	II	3	Right12 Left 12	7	Yes, ligation(+)	Yes	No	No, intestinal perforation (+)	Yes	0-86 (36)	86-100 (38)	112 (40)
125	II	3	Left 9	9	Yes	Yes	No	No	Yes	0-82 (38)	82-115 (43)	167 (50)

FT, fibrovascular tissue; PDA, patent ductus arteriosus; BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; NEC, necrotizing enterocolitis; n-CPAP, nasopharyngeal continuous positive airway pressure; PMA, postmenstrual age.

Table 7. Incidence of maximum stages of ROP: comparison with Swedish population-based study.

ROP stage	Swedish population-based cohort study Gestational age (weeks)						Present study Gestational age (weeks)						
	22	23	24	25	26	Total	22	23	24	25	26	27	Total
	(n = 5)	(n = 53)	(n = 99)	(n = 171)	(n = 178)	(n = 506)	(n = 0)	(n = 5)	(n = 8)	(n = 10)	(n = 14)	(n = 14)	(n = 51)
No ROP	0	5	14	40	79	138 (27.3%)	0	1	0	2	5	7	15 (29.4%)
ROP1	0	5	11	35	26	77 (15.2%)	0	3	2	3	5	5	18 (35.3%)
ROP2	1	10	25	41	38	115 (22.7%)	0	0	0	0	0	0	0
ROP3	4	31	47	53	35	170 (33.6%)	0	1	6	5	4	2	18 (35.3%)
ROP4A	0	0	0	1	0	1 (0.2%)	0	0	0	0	0	0	0
ROP4B	0	0	1	1	0	2 (0.4%)	0	0	0	0	0	0	0
ROP5	0	2	1	0	0	3 (0.6%)	0	0	0	0	0	0	0

ROP, retinopathy of prematurity.

weeks of postmenstrual age. This point was chosen based on both a previous epidemiological study on the incidence of ROP, and on the results from other international studies (Holmström et al. 2012; Fierson et al. 2013).

As seen in Table 5, infant no. 224 showed a poor weight gain during the early postnatal period (a chronological age of 2 months). This infant later developed severe ROP, with cataract subsequently developing in both eyes at a chronological age of 10 months. Previous studies have demonstrated that a prolonged period of a low level of serum IGF-I in preterm infants was strongly associated with ROP (Hellström et al. 2003; Löfqvist et al. 2006). Postnatal deficiencies of growth factors or nutrition can cause severe ROP. Thus, the WINROP system that utilizes postnatal weight gains in relation to IGF-I may be useful for predicting severe ROP and reducing the number of examinations (Löfqvist et al. 2006; Wu et al. 2012).

The clinical characteristics of treated infants in the current study are shown in Table 6. When extremely preterm infants were maintained using intubation and ventilation with PROP, the ROP findings were stable and their retinal vessels grew into the peripheral retina. Two previous studies have shown that the threshold levels of the partial pressure of the arterial carbon dioxide ($PaCO_2$), pH, the fraction of the inspired oxygen (FiO_2), and the SpO_2 were more stringent for the intubation group when compared to the CPAP group (Morley et al. 2008; Finer et al. 2010). Other studies have further suggested that the fluctuations between hyperoxia and hypoxia are more harmful with regard to developing severe ROP (York et al. 2004; Di Fiore et al. 2010).

In summary, the present study has demonstrated that

extremely preterm infants exhibit low incidence of sight-threatening ROP. Future prospective epidemiological studies will further clarify the natural history of ROP that occurs in extremely preterm infants with perinatal care in Japan.

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Conflict of Interest

The authors declare no competing interest.

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