ORIGINAL ARTICLE

Severe retinopathy of prematurity in infants <30 weeks' gestation in New South Wales and the Australian Capital Territory from 1992 to 2002

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Arch Dis Child Fetal Neonatal Ed 2007;**92**:F251–F254. doi: 10.1136/adc.2006.096479

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Accepted 6 January 2007
Published Online First 24 January 2007

Background: Retinopathy of prematurity (ROP) significantly increased in New South Wales (NSW) from 1986 to 1994, but more recent data suggest that there has now been a decrease.
Objective: To study the incidence and treatment of severe ROP (stage ≥3) in NSW and the Australian Capital Territory (ACT) from 1992 to 2002.
Methods: Data collected prospectively from the Neonatal Intensive Care Units' (NICUS) Data Collection over an 11-year period in infants <30 weeks' gestation were divided into four epochs and analysed retrospectively. The incidence and treatment of severe ROP were compared for gestational ages ≤24 weeks', 25–26 weeks' and 27–29 weeks' gestation over the four epochs.
Results: In infants ≤24 weeks' gestation the incidence of severe ROP and those treated increased significantly (stage ≥3: from 17 (41.5%) to 41 (53.9%), p = 0.052; treated: from 8 (19.5%) to 25 (32.9%), p<0.05 (first and fourth epoch)). In infants 25–26 weeks' gestation the incidence of severe ROP decreased significantly whereas there was a non-significant increase in those treated (stage ≥3: from 55 (26.2%) to 46 (19.3%), p<0.05; treated: from 19 (9.0%) to 32 (13.4%)). In infants 27–29 weeks' gestation, there was no significant change in the incidence of severe ROP or those treated (stage ≥3: from 30 (4.1%) to 17 (2.4%); treated: from 14 (1.9%) to 8 (1.1%)).
Conclusion: In infants ≤24 weeks' gestation there has been a significant increase in severe ROP, and in infants <27 weeks' gestation the numbers treated for severe ROP increased.

Retinopathy of prematurity (ROP) is a disease of the growing blood vessels in the retina of the immature eye and is most common in the very premature infants.[1–9] The prevention and treatment of ROP remains controversial and is the subject of much debate and multicentric trials.[10–14] There has been a shift towards the use of early lower inspired oxygen levels, lowering of oxygen saturation targets, earlier laser treatment for pre-threshold ROP and higher oxygen saturation targets in infants beyond 34 weeks' corrected gestational age at risk of developing severe ROP.[6 11–13 15–19]

The introduction of surfactant over the past two decades for the treatment of respiratory distress syndrome and an increased use of antenatal steroids has seen a marked increase in survival of the very preterm infants and thus greater number of infants at risk of ROP.[20–22] We showed there was an increased incidence of ROP in New South Wales (NSW) following the introduction of surfactant in Australia in 1991.[1 2] More recent data have suggested that over the past few years the incidence of ROP in NSW has decreased.[3]

Thus the aims of our investigation were to study the survival rate, incidence of severe ROP (stage ≥3) and treatment of ROP in NSW and the Australian Capital Territory (ACT) from 1992 to 2002.

METHODS

To determine the incidence of ROP in infants <30 weeks' gestation, we analysed data collected prospectively from the Neonatal Intensive Care Units' (NICUS) Data Collection over an 11-year period from 1992 to 2002. The NICUS data collection was established in 1985 and collects prospective data on preterm infants <32 weeks' gestation admitted to level 3 neonatal intensive care units in NSW and the ACT (see appendix 1 for the included hospitals from 1992). The 11-year period from 1992 was chosen as surfactant was introduced in Australia in July 1991. The years following this introduction would thus give an indication of the effects of surfactant on survival of the very preterm infants as well as its effect on ROP. The 11-year period was divided into four epochs to review the trend (January 1992–December 1994, January 1995–December 1997, January 1998–June 2000 and July 2000–December 2002). In the first three years (first epoch) Exosurf (an artificial surfactant; Colfosceril palmitate, Glaxo-Wellcome) was used and in the later years, Survanta (bovine surfactant; Beractant, Ross Laboratories) was introduced and has been mainly used since about 1995. The period from 1995 to 2002 was divided into three epochs to have approximately equal numbers in each group giving one three-year epoch and two 2.5-year epochs. The infants were grouped by gestational age (22–24 weeks', 25–26 weeks' and 27–29 weeks' gestation) and a birth weight group of <1000 g. Survival rate, incidence of severe ROP (stage ≥3) and those treated (cryotherapy or laser therapy) were compared for each infant group over the four epochs.

We used the international classification of ROP for staging,[23 24] and for the purposes of this study we included infants with stage ≥3—that is:

- Stage 3—ridge with extraretinal fibrovascular proliferation
- Stages 4 and 5—subtotal or total retinal detachment (considered as one group for this study)

Each hospital had its own ophthalmic schedule, technique and time of initial examination, which ranged from four to six weeks' postnatal age or from 31 to 33 weeks' corrected

Abbreviations: ACT, Australian Capital Territory; NSW, New South Wales; ROP, retinopathy of prematurity

Table 1 Survival and examined for retinopathy of prematurity by gestational age groups and time epoch. Values are n/N (%)

Gestational age	1992–94	1995–97	1998–2000	2000–02
22–24 weeks				
Survived	41/95 (43.2)*	53/125 (42.4)	55/142 (38.7)	76/168 (45.2)
Examined	41/41 (100)†	53/53 (100)	54/55 (98.2)	76/76 (100)
25–26 weeks				
Survived	210/333 (63.1)	268/386 (69.4)	249/348 (71.6)**	238/331 (71.9)‡**
Examined	208/210 (99.0)	267/268 (99.6)	248/249(99.6)	236/238(99.2)
27–29 weeks				
Survived	729/833 (87.5)	737/813 (90.7)§	747/810 (92.2)**	707/780 (90.6)‡§
Examined	645/729 (87.0)	684/737 (92.3)**	726/747 (97.1)**	676/707 (95.4)¶**

*Survived/total admissions (percent survival); †examined/survived (percent examined).
‡Significant trend for increased survival from 1992–94 to 2000–02 ($p<0.02$); ¶significant trend for increased examined from 1992–94 to 2000–02 ($p<0.01$); §significantly different from 1992–94 epoch ($p<0.05$) and **($p<0.02$).

gestational age. Re-examinations depended on the gestational age of the infant and the stage of ROP. These data are routinely collected and anonymised for audit purposes, thus ethical approval was not sought.

Statistical analysis

We used logistic regression to study the changes over time, with post hoc analysis to identify significant changes in individual epochs (SPSS Version 12).

RESULTS

In infants ⩽24 weeks' gestation there was no change in survival over time, but there was an increase in the total number of infants resuscitated and admitted (table 1). All but one infant in the 11-year period was examined for ROP (table 1). Table 2 shows that the incidence of severe ROP and those treated significantly increased over the 11 years ($p = 0.052$ and $p<0.05$, respectively). Of those who developed stage ⩾3 ROP there was a non-significant increase in those treated (table 2). There was no significant change in the number of infants with detached retinas over time (table 3).

In infants 25–26 weeks' gestation there was a significant increase in survival over time (table 1, $p<0.02$). Over the 11 years six infants were not examined for ROP, and these were spread evenly over each epoch (table 1). The incidence of severe ROP decreased significantly ($p<0.05$), but there was a non-significant increase in those treated in the last epoch (table 2). Of those who developed stage ⩾3 ROP, however, there was a significant increase in those treated over time (table 2, $p<0.02$). There was no significant change in the number of infants with detached retinas over time (table 3).

In infants 27–29 weeks' gestation there was a significant increase in survival over time (table 1, $p<0.02$). The proportion of infants examined significantly increased over the four epochs (table 1, $p<0.02$). The incidence of severe ROP significantly decreased in the second epoch ($p<0.05$) and remained stable over the subsequent epochs whereas there was a non-significant decrease in treated infants in the second epoch that remained stable in subsequent epochs (table 2). Of those who developed stage ⩾3 ROP there was no change in those treated over time (table 2). There was rise in the proportion of small for gestational age (SGA (<10th birth weight centile)) infants over the four epochs who developed severe ROP (3/30 (10%), 1/15 (6.7%), 4/19 (21.1%) and 4/17 (23.5%), respectively (number in parenthesis represents the percent of those with severe ROP)). There was no significant change in the number of infants with detached retinas over time (table 3).

From 1992 to 2002 the proportion of infants <1000 g who developed severe ROP significantly increased (89/102 (87.3%), 81/87 (93.1%), 79/83 (95.2%) and 101/104 (97.1%), respectively, $p = 0.005$) (number in parenthesis represents the percent of all infants with severe ROP)).

Of those infants <1000 g who survived, there was a non-significant increase in treated infants, but of those who developed stage ⩾3 ROP there was a significant increase in treated infants over time (table 4, $p<0.05$). There was no significant change in the proportion of SGA infants in those infants <1000 g who developed severe ROP (3/89 (3.4%), 3/81 (3.7%), 6/79 (7.6%) and 4/101 (4.0%), respectively) over time.

Table 2 Retinopathy of prematurity stage ⩾3 and those treated by gestational age groups and time epoch. Values are n/N (%)

Gestational age	1992–94	1995–97	1998–2000	2000–02
22–24 weeks				
Stage ⩾3	17/41 (41.5)*	16/53 (30.2)	23/55 (41.8)	41/76 (53.9)‡
Treated/survived	8/41 (19.5)*	9/53 (17.0)	15/55 (27.3)	25/76 (32.9)‡
Treated/stage ⩾3	8/17 (47.1)†	9/16 (56.3)	15/23 (65.2)	25/41(61.0)
25–26 weeks				
Stage ⩾3	55/210 (26.2)	56/268 (20.9)	41/249 (16.5)††	46/238 (19.3)¶
Treated/survived	19/210 (9.0)	21/268 (7.8)	24/249 (9.6)	32/238 (13.4)
Treated/stage ⩾3	19/55 (34.5)	21/56 (37.5)	24/41 (58.5)††	32/46 (69.6)§††
27–29 weeks				
Stage ⩾3	30/729 (4.1)	15/737 (2.0)**	19/747 (2.5)	17/707 (2.4)
Treated/survived	14/729 (1.9)	7/737 (0.9)	8/747 (1.1)	8/707 (1.1)
Treated/stage ⩾3	14/30 (46.7)	7/15 (46.7)	8/19 (42.1)	8/17 (47.1)

All results are expressed total survivors unless indicated.
*Stage ⩾3/survived (percent with stage ⩾3) or treated/survived (percent treated); ††treated/stage ⩾3 (percent treated).
‡Significant trend to increased stage ⩾3 and treated ($p = 0.052$ and $p<0.05$, respectively); ¶significant trend to decreased stage ⩾3 ($p<0.05$); §significant trend to increased treated of those who developed stage ⩾3 ($p<0.001$);
**significantly different from 1992–94 epoch ($p<0.05$) and ††($p<0.02$).

Table 3 Stages 4 and 5 retinopathy of prematurity (ROP) by gestational age groups and time epoch

Gestational age	1992–94	1995–97	1998–2000	2000–02
22–24 weeks				
Stage ⩾4/survived	0/41 (0)*	2/53 (3.8)	1/55 (1.8)	3/76 (3.9)
Stage ⩾4/stage ⩾3	0/17 (0)†	2/16 (12.5)	1/23 (4.3)	3/41 (7.3)
25–26 weeks				
Stage ⩾4/survived	2/210 (1.0)	1/268 (0.4)	2/249 (0.8)	3/238 (1.3)
Stage ⩾4/stage ⩾3	2/55 (3.6)	1/56 (1.8)	2/41 (4.9)	3/46 (8.7)
27–29 weeks				
Stage ⩾4/survived	5/729 (0.7)	0/737 (0)	2/747 (0.3)	0/707 (0)
Stage ⩾4/stage ⩾3	5/30 (16.6)	0/15 (0)	2/19 (10.5)	0/17 (0)

All results are expressed as total survivors.
Values are n/N (%).
*Stage ⩾4 ROP/survived (percent survival); †stage ⩾4 ROP/stage ⩾3 (percent of severe ROP).

Table 4 Survival and stage ⩾3 by birth weight <1000 g and time epoch

Birth weight	1992–94	1995–97	1998–2000	2000–02
<1000 g				
Survived	413/623 (66.3)*	476/680 (70.0)	453/653 (69.4)	467/669 (69.8)
Stage ⩾3	89/413 (21.5)†	81/476 (17.0)	79/453 (17.4)	101/467 (21.6)
Treated/survived	37/413 (9.0)	39/476 (8.2)	45/453 (9.9)	62/467 (13.3)
Treated/stage ⩾3	37/89 (41.6)	39/81 (48.1)	45/79 (57.0)	62/101 (61.4)‡

Values are n/N (%).
*Survived/total admissions (percent survival); †stage ⩾3/survived (proportion with stage ⩾3).
‡Significant trend to increased treated ($p<0.05$).

What is already known on this topic

- Small preterm infants are more susceptible to severe ROP
- Treatment of severe ROP with cryotherapy or laser therapy improves long-term visual outcome

What this study adds

- In infants ⩽24 weeks' gestation, severe ROP has significantly increased and occurred in >50% of survivors in the period 2000 to 2002
- In infants <27 weeks' gestation and/or <1000 g, >60% of infants who develop severe ROP were treated with laser therapy in the period 2000 to 2002

DISCUSSION

We found significant changes in the incidence of severe ROP between 1992 and 2002. This has been due to the increase in severe ROP in the infants of gestational ages 22–24 weeks. More than 50% of surviving infants in this group developed severe ROP in 2000–02. In contrast, in infants of 25–26 weeks' and 27–29 weeks' gestation there was a decrease in severe ROP. Thus the rise in severe ROP in infants <27 weeks' gestation that we previously found in NSW[1 2] has been sustained, but is now in the very premature infants. It was encouraging that retinal detachment (stages 4 and 5 ROP) remained low in all groups.

Gestational age band-specific differences in the incidence of ROP are well described.[1–9 14] Data from the Australian and New Zealand Neonatal Network (ANZNN) showed that in 1998–1999 the incidence of severe ROP was 33.6% and 12.9% for the 22–24 weeks' and 25–26 weeks' gestation infants, respectively.[9] Similar results have been found in the UK and North America.[7 14] The gestational age difference is not surprising as ROP is a disease of the developing retinal blood vessels and in lower gestational age infants' these growing vessels are ''far back'' in the retina.[5 23–25] This trend towards increased severe ROP over the past few years in the immature babies is a disturbing feature of this analysis and has been found by others.[26] Although factors such as observer and surveillance biases, enhanced screening, and technical improvements in ophthalmology may have also contributed to this increase, it is feasible that these data represent a true increase in the incidence severe ROP in the most preterm groups of infants.

The number of infants born live ⩽24 weeks' gestation in NSW and ACT increased from 95 to 120 a year over the study period. There was a significant increase in the proportion of infants admitted to neonatal intensive care from 33.5% to 56.2% ($p<0.01$).[27] Factors contributing to this increase in the overall numbers include: (1) an increase in in-utero transfers from peripheral hospitals to level 3 intensive care units, and (2) increased use of antenatal steroids and introduction of surfactant leading to more attempts at resuscitation. However, survival until hospital discharge for these premature infants did not improve over this period (table 1). The increased incidence of severe ROP may be due to sicker smaller infants surviving. Although survival until hospital discharge increased in infants 25–26 and 27–29 weeks' gestation between 1992 and 2002, this was not associated with an increase in severe ROP.

In conjunction with the above changes we also found significant changes dependent on gestational age in the number of infants treated for severe ROP (table 2), consistent with reports from other networks.[7 14] More than 60% of infants <27 weeks' gestation and/or <1000 g were severe ROP were treated with cryotherapy or laser therapy. Cryotherapy for threshold ROP has been shown to curtail altered vasculogenesis and significantly improves the outcome up to 15 years.[10] Laser therapy has now become the treatment of choice and was in place in the second epoch in NSW (Dr John Kennedy, personal communication, 2006). Infants are now being treated earlier when the disease is at a ''pre-threshold'' stage.[11] Pre-threshold treatment of severe ROP probably had little influence on the overall increase in treated infants in this study and may simply be the increased competence and ease of use of laser therapy with fewer postoperative complications.

In conclusion, we have shown that in NSW and the ACT from 1992 to 2002, there were significant increases in both severe ROP and those treated for ROP in the very preterm infants (⩽24 weeks' gestation, $p = 0.052$ and $p<0.05$, respectively). In infants 25–26 weeks' gestation, although severe ROP has decreased significantly ($p<0.05$), those treated has increased. In infants 27–29 weeks' gestation, the incidence of severe ROP has decreased. Screening programmes for ROP should continue to include these more mature infants of 27–29 weeks' gestation.

ACKNOWLEDGEMENTS

We thank Dr Elizabeth John and Associate Professor William McGuire for their useful suggestions to the manuscript, Dr Karen Byth for performing the statistical analysis and Barbara Bajuk for supplying the combined records of 1992–2002 NSW and ACT midwives data. We thank the participating NICUs listed in the appendix for providing the data and the ophthalmologists who examined the infants. We also thank the clinical audit officers for extracting the data.

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Competing interests: None declared.

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APPENDIX 1: PARTICIPATING HOSPITALS

- 1992
  - John Hunter Children's Hospital (Newcastle)
  - Nepean Hospital
  - Royal Hospital for Women
  - Royal Prince Alfred Women & Babies Hospital
  - Royal North Shore Hospital
  - Sydney Children's Hospital
  - The Children's Hospital Westmead
  - Westmead Hospital, Women and Babies Unit
- 1994
  - Liverpool Hospital
- 1995
  - The Canberra Hospital