RESEARCH PAPER

Role of antenatal corticosteroids in retinopathy of prematurity among preterm neonates at a tertiary-care neonatal intensive care unit in North India: a prospective observational study

Running title: *Antenatal corticosteroids and retinopathy of prematurity*

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Abstract

Background: Retinopathy of prematurity (ROP) is a leading cause of preventable childhood blindness in low- and middle-income countries. Antenatal corticosteroids (ANS) are routinely used to reduce neonatal respiratory and intracranial morbidity, but their effect on ROP is less well characterised in Indian neonatal cohorts. We examined the association between ANS exposure and ROP, both in unadjusted analysis and after adjustment for major postnatal risk factors.

Methods: A hospital-based prospective observational study was conducted in the neonatal intensive care unit (NICU) of a tertiary-care teaching hospital in North India between April 2024 and October 2025. One hundred inborn preterm neonates with birth weight <2000 g and gestational age <34 weeks, and those of 34–36 weeks with predefined RBSK risk factors, were screened for ROP according to the International Classification of Retinopathy of Prematurity (ICROP-3). Maternal ANS exposure and neonatal morbidities were recorded. Associations were assessed by chi-square tests and multivariable logistic regression in SPSS v28.0, with $p \leq 0.05$ considered significant.

Results: The overall incidence of ROP was 11% (11/100). Zone 2 disease (63.6%) and stages 2–3 (5% each) predominated; aggressive ROP occurred in 1%. ANS had been administered to 64/100 mothers (64%). ROP occurred in 3/64 (4.7%) neonates exposed to ANS versus 8/36 (22.2%) unexposed ($p < 0.001$). Lower gestational age ($p = 0.034$), lower birth weight ($p < 0.001$), oxygen therapy ($p = 0.012$), mechanical ventilation ($p < 0.001$), sepsis ($p < 0.001$) and anaemia ($p < 0.001$) were also significantly associated with ROP. On multivariable logistic regression, ANS exposure remained an independent protective factor against ROP ($B = –3.760$; OR = 0.023; $p = 0.020$); mechanical ventilation was of borderline significance ($p = 0.066$).

Conclusion: In this North-Indian tertiary-care cohort, completion of antenatal corticosteroid therapy was independently associated with a substantially lower risk of ROP. The finding supports universal, timely antenatal corticosteroid use in mothers at risk of preterm delivery, alongside judicious oxygen administration, prevention of sepsis and management of anaemia.

Keywords: Retinopathy of prematurity; Antenatal corticosteroids; Preterm neonate; Neonatal intensive care unit; Risk factors; India.

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Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder of the developing retina that occurs almost exclusively in preterm infants with incompletely vascularised retinae. It remains a leading cause of preventable childhood blindness, particularly in countries undergoing rapid expansion of neonatal intensive care without proportional growth in screening services.1,2

Premature birth interrupts retinal vasculogenesis. The relatively hyperoxic extrauterine environment, together with falling levels of insulin-like growth factor-1 and vascular endothelial growth factor (VEGF), produces an initial phase of vaso-attenuation; subsequent retinal hypoxia drives disorganised VEGF expression and pathological neovascularisation.3,4 The clinical course of ROP varies widely, from spontaneous regression to tractional retinal detachment and blindness if untreated. India contributes one of the largest absolute burdens of ROP globally because of its high preterm birth rate and the steady improvement in survival of very-low-birth-weight infants — a phenomenon described as a 'third epidemic' of ROP in middle-income countries.5,6 Reported incidence in Indian studies has ranged from 8% to over 40% depending on inclusion criteria, the proportion of extremely preterm infants surviving, and screening practice.7–9

Antenatal corticosteroids (ANS) given to mothers at risk of preterm delivery accelerate fetal lung maturation and reduce respiratory distress syndrome, intraventricular haemorrhage and neonatal mortality. By modulating these downstream morbidities — and the corresponding need for prolonged oxygen exposure and mechanical ventilation — ANS may plausibly reduce the incidence of ROP. Evidence on this question, however, has been inconsistent: while a Brazilian cohort by Freitas et al. identified antenatal corticosteroids as a significant predictor of ROP,10 few prospective Indian studies have specifically evaluated ANS exposure as a determinant of ROP using multivariable analysis.

The present study was conducted at a tertiary-care NICU in North India to determine the incidence of ROP among screened preterm neonates and, in particular, to examine the role of antenatal corticosteroid administration as a determinant of ROP after adjusting for major postnatal risk factors.

Materials and Methods

Study design and setting

This was a single-centre, hospital-based, prospective observational study conducted in the level-III neonatal intensive care unit (NICU) of the Department of Paediatrics, Maharishi Markandeshwar Institute of Medical Sciences and Research (MMIMSR), Mullana, Ambala, Haryana, India, between April 2024 and October 2025.

Participants

All inborn preterm neonates admitted to the NICU during the study period who met the screening criteria recommended by the Rashtriya Bal Suraksha Karyakram (RBSK) were considered eligible: birth weight <2000 g and gestational age <34 weeks, and neonates of 34–36 weeks with one or more additional risk factors (need for respiratory support in the neonatal period, oxygen therapy for more than 6 hours continuously, episodes of apnoea, blood or exchange transfusion, surfactant administration, septicaemia, intraventricular haemorrhage, patent ductus arteriosus or metabolic acidosis). Neonates with congenital cataract or major congenital malformations of the eye, outborn babies, and those whose parents declined consent were excluded. A convenience sample of 100 neonates was recruited, accounting for losses due to mortality and discharge against medical advice.

Definitions and variables

Gestational age was determined from the best obstetric estimate using the last menstrual period, first-trimester ultrasound and the new Ballard score, as available. Birth weight was recorded within one hour of birth. Antenatal corticosteroid exposure was recorded from maternal case notes and dichotomised as 'received' (any documented dose) or 'not received'. Postnatal exposures and morbidities — oxygen therapy by hood, prongs, CPAP or mechanical ventilation; surfactant administration; respiratory distress syndrome (RDS); culture-positive or clinical sepsis; anaemia (defined per institutional NICU protocol); intraventricular haemorrhage (IVH); patent ductus arteriosus (PDA); necrotising enterocolitis (NEC); apnoea of prematurity (AOP); and packed-cell transfusion — were recorded throughout the NICU stay.

ROP screening and classification

Ophthalmological examination was performed by an ophthalmologist using indirect ophthalmoscopy after pupillary dilatation. ROP was diagnosed and staged according to the International Classification of Retinopathy of Prematurity (ICROP-3), and zone, stage, plus disease and aggressive ROP were recorded.11 Treatment-requiring (Type 1) and observation-only (Type 2) disease were classified per the Early Treatment for Retinopathy of Prematurity (ETROP) criteria. Indicated cases received laser photocoagulation of the avascular retina.

Ethics

The study protocol was approved by the Institutional Ethics Committee, MMIMSR, Mullana (Project No. IEC-3238). Written informed consent was obtained from a parent or legal guardian before any study procedure.

Statistical analysis

Data were entered in Microsoft Excel and analysed using SPSS v28.0 (IBM, Armonk, NY). Continuous variables were summarised as mean ± standard deviation and categorical variables as frequencies and percentages. Associations between categorical risk factors and ROP were tested with the chi-square test. A multivariable logistic regression model was fitted to identify independent predictors of ROP, with variables entered based on prior clinical plausibility and univariate significance. Variables with quasi-complete separation or sparse cell counts were noted and excluded from the regression solution. A two-sided $p \leq 0.05$ was considered statistically significant.

Results

Cohort characteristics

During the study period 4350 deliveries occurred at the institution; 26 (0.6%) infants had a birth weight ≤1000 g and 4324 (99.4%) >1000 g. One hundred eligible inborn preterm neonates were enrolled. Among these, 6 (6%) were ≤28 weeks of gestation, 16 (16%) were 28^{+1}–30 weeks, 33 (33%) were 30^{+1}–32 weeks, 25 (25%) were 32^{+1}–34 weeks and 20 (20%) were >34 weeks. Four (4%) weighed ≤1000 g, 30 (30%) weighed 1001–1500 g and 66 (66%) weighed 1500–2000 g. Fifty-four (54%) were male and 46 (46%) female.

Incidence, zone and stage of ROP

Any ROP (≥ stage 1) was detected in 11 of 100 neonates, giving an incidence of 11%. Among the 11 affected neonates, Zone 1, 2 and 3 involvement was seen in 2 (18.2%), 7 (63.6%) and 2 (18.2%) respectively. Stage 1 ROP was observed in 3, stage 2 in 5, stage 3 in 5 and aggressive ROP in 1 neonate. Plus disease was present in 3 (27.3%) and absent in 8 (72.7%) affected neonates. No infant developed stage 4 or 5 disease. Laser photocoagulation was required in 4 of 11 (36.4%) affected infants; the remaining 7 (63.6%) regressed with observation.

Antenatal corticosteroid exposure and ROP

Sixty-four (64%) of the 100 mothers had received antenatal corticosteroids; 36 (36%) had not. The incidence of ROP was substantially higher among neonates unexposed to ANS than among those exposed.

Antenatal corticosteroid exposure	With ROP, n (%)	Without ROP, n (%)	p-value
Not administered (n = 36)	8 (72.8)	28 (31.5)	< 0.001
Administered (n = 64)	3 (27.2)	61 (68.5)	

Other risk factors

Univariate associations with ROP were observed for lower gestational age ($p = 0.034$) and lower birth weight ($p < 0.001$). All 11 ROP-affected neonates received oxygen support (vs 45/89, 50.6%; $p = 0.012$) and 8 (72.8%) required mechanical ventilation (vs 28/89, 31.5%; $p < 0.001$). Sepsis was present in all ROP cases (vs 15/89, 16.9%; $p < 0.001$) and anaemia in 8 (72.8%) (vs 28/89, 31.5%; $p < 0.001$). Gender, RDS, PDA, NEC, IVH, AOP, surfactant administration and packed-cell transfusion were not significantly associated with ROP.

Multivariable analysis

Variable	β	Odds ratio (Exp β)	p-value
Antenatal corticosteroid use	-3.760	0.023	0.020
Mechanical ventilation	3.684	0.025	0.066
Oxygen support	2.092	8.101	0.439
Apnoea of prematurity	2.261	0.104	0.228
Blood transfusion	1.060	2.886	0.662
Intraventricular haemorrhage	0.985	2.677	0.709
Necrotising enterocolitis	0.652	1.920	0.759

In the multivariable logistic regression model, antenatal corticosteroid exposure was the only variable that retained statistical significance and acted as an independent protective factor against ROP ($\beta = -3.760$; OR = 0.023; $p = 0.020$). Mechanical ventilation showed a borderline association ($p = 0.066$). Oxygen support, NEC, IVH, blood transfusion and apnoea of

prematurity were not independently associated with ROP. Sepsis, surfactant use, RDS, PDA and laser therapy yielded unstable parameter estimates because of sparse cell counts and quasi-complete separation, and reliable odds ratios could not be derived for these variables.

Discussion

In this prospective single-centre cohort of 100 inborn preterm neonates from a tertiary-care NICU in North India, the incidence of any ROP was 11%, and antenatal corticosteroid exposure was independently associated with a markedly lower risk of ROP after adjustment for the major postnatal risk factors. To our knowledge this is one of the few prospective Indian studies to evaluate antenatal corticosteroid exposure as an a priori secondary objective in ROP epidemiology.

The observed 11% incidence is at the lower end of contemporary Indian estimates. Sheth et al. reported 8% in a tertiary-care unit,7 and Anupama et al. 18.7% in coastal South India,12 while higher rates have been reported by Sharma et al. (42.1%) in Himachal Pradesh,8 Shivananda et al. (46.7%) in Karnataka13 and Jothi et al. (54.8%) in Tamil Nadu.14 Differences are attributable to the proportion of extremely preterm and extremely low-birth-weight neonates surviving long enough to be screened, oxygen-administration practice and screening cut-offs. In our cohort only 4% of infants weighed ≤1000 g and 6% were ≤28 weeks, which probably contributed to the comparatively low incidence and to the absence of stages 4–5 disease.

The principal finding of this study is the independent protective association of antenatal corticosteroids with ROP. The incidence of ROP was 4.7% among neonates whose mothers received ANS compared with 22.2% among those whose mothers did not ($p < 0.001$), and ANS retained statistical significance in the multivariable model (OR = 0.023; $p = 0.020$). This finding is consistent with the prospective cohort of Freitas et al., who identified antenatal corticosteroids as one of several independent predictors of ROP in Brazil,10 and is biologically plausible. Antenatal corticosteroids reduce respiratory distress syndrome, the need for surfactant, intraventricular haemorrhage and the duration and intensity of supplemental oxygen — all factors that drive the hyperoxic phase of ROP pathogenesis and the subsequent hypoxia-driven VEGF surge.3,4 In addition, glucocorticoid exposure may modulate the VEGF–IGF-1 axis directly and influence postnatal vascular maturation. Several earlier Indian and international studies that focused on postnatal risk factors did not include ANS as an exposure of interest,9,15–18 which may partly explain the relative paucity of multivariable evidence for this association in the regional literature.

Other risk factors identified in our cohort — lower gestational age, lower birth weight, supplemental oxygen, mechanical ventilation, sepsis and anaemia — are well established and consistent with the wider literature.8,9,12–18 In our regression model, sepsis, RDS, PDA, surfactant and laser therapy could not be evaluated reliably because all 11 ROP cases were positive for sepsis and other cells were sparsely populated, producing quasi-complete separation. This is a recognised limitation of regression with small numbers of events19 rather than evidence against a true association, and it should be interpreted as a constraint of statistical methodology, not as a clinical exoneration of these risk factors.

Mechanical ventilation showed a borderline independent association in the present cohort, consistent with reports from Vietnam16 and Iran,20 and the larger univariate effect ($p < 0.001$) suggests the borderline regression result is plausibly limited by sample size. Anaemia and sepsis, which were strongly associated on univariate analysis, are increasingly recognised as drivers of severe ROP because of their effects on retinal oxygen delivery and systemic inflammation respectively.

The strengths of this study include its prospective design, standardised ICROP-3 screening,11 simultaneous collection of antenatal and postnatal variables, and the use of multivariable logistic regression to evaluate ANS as an a priori secondary outcome. Limitations are also acknowledged. The sample size was modest, with only 11 ROP events; this limited statistical power and produced sparse-cell instability in the regression model. Antenatal corticosteroid exposure was treated as a dichotomous variable; the dose, completeness of the course and time-to-delivery interval — all known to modify efficacy — could not be analysed separately. As a single-centre study confined to inborn neonates, generalisability to other settings and to outborn referrals is limited. Long-term visual outcomes were not assessed.

Despite these limitations, the magnitude and direction of the association observed are consistent with the established neonatal benefits of antenatal corticosteroids and reinforce the recommendation to administer a complete course of antenatal corticosteroids to all women at risk of preterm delivery between 24 and 34 weeks. From an ROP-prevention standpoint, ANS appears to act upstream of the postnatal risk-factor chain — by reducing severity of respiratory illness and the need for intensive oxygen therapy — and may therefore complement, rather than replace, standard preventive practices of judicious oxygen administration, infection control, anaemia management and timely ROP screening.

Conclusion

In this prospective tertiary-care cohort from North India, the incidence of retinopathy of prematurity was 11%, and the completion of antenatal corticosteroid therapy was associated with an independent and substantial reduction in the risk of ROP. The findings

support the universal and timely use of antenatal corticosteroids in mothers at risk of preterm delivery, combined with strict oxygen monitoring, prevention and treatment of sepsis and anaemia, and standardised ROP screening, as a coherent strategy for reducing the burden of preventable preterm-related blindness in India.

Declarations

Ethics approval and consent: Approved by the Institutional Ethics Committee, MMIMSR, Mullana (Project No. IEC-3238). Written informed consent was obtained from a parent or guardian of every neonate.

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Conflicts of interest: The authors declare no conflicts of interest.

Author contributions: YPKR conceived the study, collected data, performed analysis and drafted the manuscript. BM supervised the study and revised the manuscript critically. MLP supervised the ophthalmological component and revised the manuscript. All authors approved the final version.

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