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Dopamine and Indomethacin: Independent Risk Factors for Threshold Retinopathy of Prematurity?

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Aim: **To assess whether dopamine and indomethacin prescribed in the first week of life are indicators and independent risk factors to develop threshold retinopathy of pregnancy (ROP) during later neonatal stay.**

Methods: **In a case-control approach, the perinatal characteristics of infants who developed threshold ROP (*n*=31) were compared with control infants of the same gestational age (GA). A multiple regression model (MedCalc®) was used in an attempt to document independency of these risk factors when controlled for other markers of severity of disease.**

Results: **Birth weight, incidence of SGA (small-for-gestational-age), mean CRIB (Clinical Risk Index for Babies) score, mean OI (oxygenation index) and mean MAP (mean airway pressure) were significantly different between cases and controls (*P*<0.05). There was no significant difference in the prescription of dopamine between cases and controls, but maximal dose in the first day, the first week and length of treatment in the first week of life were significantly different between cases and controls (*P*<0.05). Indomethacin was significantly more often prescribed in infants who developed threshold ROP during later neonatal stay (*P*<0.05). After correction for any other documented indicator (CRIB, OI or MAP) of severity of disease at birth, dopamine and indomethacin were no longer independent risk factors for threshold ROP.**

Conclusions: **Dopamine and indomethacin are indicators of an increased risk to develop threshold ROP but are not independent risk factors after correction for any other marker of disease severity at birth. Since there are differences in prescriptive behaviour between different units, it may be relevant to use more objective markers of disease severity (CRIB, OI, MAP) to further delineate the relative risk already associated with a given GA in order to develop a weighted risk score.**

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Introduction

Retinopathy of prematurity (ROP) is an important outcome variable of morbidity at discharge, especially in extreme low birth weight infants (ELBW infants, birthweight <1000 g) and is still an important cause of visual impairment and blindness in childhood[1]. As well as birth weight and gestational age (GA) as major risk factors, there are reports in the literature on the effect of duration of respiratory disease, perinatal growth characteristics, maternal disease, number or volume of transfusions administered or prescribed medications (dopamine, indomethacin)[2–10]. Effective treatment depends on early and accurate recognition of those infants at highest risk to develop ROP. Additional indicators besides birth weight or GA might be used to further discriminate the relative risk to develop ROP already associated with a given GA or birth weight in order to develop a weighted risk score.

In this paper, we focus on prescribed medications (dopamine, indomethacin) in the first week of life and their associated risk to develop threshold ROP. Clinical characteristics and markers of disease severity at birth were also documented in an attempt to assess whether these medications were independent risk factors for threshold ROP.

Patients and methods

The Neonatal Intensive Care Unit (NICU) of the University Hospitals, Gasthuisberg, Leuven serves as a tertiary neonatal intensive and high care unit with a capacity of 35 beds within a structured regional referral centre. During the period studied (1996–2000) 571 infants had a birth weight below 1500 g on admission. Overall survival was 85% (485/571) (54% in infants < 25 weeks GA and 92% in infants of 30 weeks GA).

Thirty-one infants developed threshold ROP, i.e. at least five contiguous or eight cumulative clock hours of stage 3 ROP in zone 1 or 2 in the presence of Plus disease[11]. The incidence of threshold ROP in the unit during this period was 6.4% in survivors with a birth weight below 1500 g.

Potential perinatal risk factors as reported in the literature and already available in the first week of life were extracted from a prospectively collected EpiInfo-database or were collected from the nursing progress reports. Data of interest in this study were birth weight (g), incidence of small-for-gestational age (SGA, i.e. < 10th percentile), associated maternal disease (pre-eclampsia or hypertension), prenatal administration of steroids (yes/no), CRIB (Clinical Risk Index for Babies) score, highest mean airway pressure (MAP) in the first 24 hours of life and highest oxygenation index (OI = highest MAP 100 FiO_2/paO_2), use of dopamine in the first week of life (Y/N), duration of treatment in the first week (hours, 0–168), and maximal dose (microg/kg/min) administered in the first 24 hours and the first week of life[12].

During this period, indomethacin (5 100 microg/kg/day) was the preferred treatment in the unit to induce closure of the patent ductus arteriosus (PDA). Indomethacin was only prescribed in symptomatic infants after echocardiography. Indomethacin was prescribed in 77/571 (13%) admitted infants with a birth weight below 1500 g. Surgical clipping was performed in 16 of these infants. There was no prophylactic use of indomethacin and administration was postponed in infants with oliguria.

Dopamine administration was based on documented intra-arterial blood pressure values. The aim was to reach a mean blood pressure of at least the gestational age (25–30 mmHg). Finally,

data on the duration of ventilation, respiratory support and supplemental oxygen (days) were collected.

These data were collected in all infants (n=31) who developed threshold ROP and were compared in a case-control approach with matched infants of the same GA, admitted in the same unit and discharged alive. GA was calculated by ultrasound data before 20 weeks GA or if not available, was based on the mother's last menstrual period or on neonatal clinical findings. This approach was also used to describe perinatal growth characteristics and its associated risk to develop threshold ROP in the same cohort[9].

Data were analysed by chi-square analysis, Wilcoxon test or Student's t-test and were expressed as mean ± standard deviation (SD) or incidence. Indicators of disease severity and prescribed medications in the first week of life – if significant in monovariate analysis – were entered in a multiple regression model (MedCalc®). A P-value of less than 0.05 was considered significant.

Results

General data

Retinopathy (any stage below threshold retinopathy) was documented in 16 (52%) of 31 control infants. Six (19%) of these control infants developed grade 3 retinopathy. The mean GA was 25 weeks in both groups (NS). The mean birth weight in threshold ROP infants was 760 g. In GA-matched controls, the mean birth weight was 906g (P<0.05). SGA (below 10th percentile) was documented in 11 (35%) of threshold ROP infants and in 4 (13%) of control infants (P<0.05). The mean duration of ventilation (27 versus 13.5 days), mean duration of respiratory support (55.3 versus 39.8 days) and mean duration of supplemental oxygen (63.8 versus 49.3 days) were significantly higher in threshold ROP infants (P<0.05) (Table 1).

Specific risk factors investigated

Associated maternal vascular disease was documented in 19 (61%) threshold ROP infants

Table 1. Perinatal characteristics in threshold ROP infants (n=31) and in GA-matched controls in the Gasthuisberg cohort

	ROP Infants	Controls	
GA at birth (weeks)	25 ± 1.4	25 ± 1.7	NS
Birth weight (g)	760 ±181	906 ±240	P<0.02
SGA	35%	13%	P<0.04
Duration of ventilation (d)	27 ±18.9	13.5 ± 3.8	P<0.004
Duration of resp support (d)	55.3 ± 23	39.8 ± 18.6	P<0.006
Duration of suppl oxygen (d)	63.8 ± 28.9	49.3 ± 21	P<0.04
Maternal disease	61%	55%	NS
Prenatal steroids	64%	51%	NS
CRIB Score	7.6 ± 3.6	4.9 ± 3.4	P<0.005
OI	13.9 ± 8.1	5.8 ± 5.6	P<0.002
MAP (cmH_2O)	14.1 ± 4.8	10 ± 5.2	P<0.01
Dopamine any use	87%	77%	NS
Max dose 0–24 h (microg/kg/min)	10 ± 4	8 ± 4	P<0.02
Max dose 0–7 days (microg/kg/min)	12 ± 5	8 ± 5	P<0.02
Duration of dopamine (h)	92 ± 59	42 ± 48	P<0.03
Indomethacin any use	55%	19%	P<0.02

Results are reported by mean and standard deviation or as incidence.(GA= gestational age, SGA= small for gestational age, CRIB= Clinical Risk Index for Babies, OI= oxygenation index, MAP= mean airway pressure)

and in 17 (55%) controls (NS). Prenatal steroids were administered in 20 (64%) threshold ROP infants and in 16 (51%) controls (NS). The mean CRIB score was 7.6, mean maximal OI was 13.9 and mean MAP was 14.1 in threshold ROP infants. In controls, the mean CRIB score was 4.9, mean maximal OI was 5.8 and mean MAP was 10. All these indicators of intensity of disease were significantly higher in infants who developed threshold ROP during later neonatal stay ($P<0.01$). Dopamine was prescribed during the first week of life in 27 (87%) of threshold ROP infants and in 24 (77%) controls (NS). The mean maximal dose in the first day of life and in the first week of life was 10 microg/kg/min and 12 microg/kg/min in threshold ROP infants. In controls, the mean maximal dose for both periods was 8 microg/kg/min ($P<0.05$). The mean length of administration was significantly longer in threshold ROP infants (92 versus 42 hours) ($P<0.05$). Indomethacin was prescribed in 17 (55%) threshold ROP infants and in 6 (19%) control infants ($P<0.05$) (Table 1). Surgical clipping of the PDA was performed in four cases and two controls.

After controlling in a multiple regression model for either CRIB score, OI or MAP, the characteristics of dopamine administration (length, mean maximal dose) were no longer an independent risk factor to develop threshold ROP. The same effect was documented for indomethacin.

Discussion

The incidence and general characteristics (birth weight, gestational age and respiratory characteristics in infants who develop threshold ROP in this cohort is very much in line with other cohorts described in literature[2-10, 13-15]. We therefore believe that this is a representative cohort.

Besides markers of the severity of disease (CRIB, OI, MAP), the maximal dose and length of administration of dopamine in the first week of life and the use of indomethacin were significantly higher in infants who developed threshold ROP during later neonatal stay. They serve as indicators of the increased risk to develop threshold ROP in this cohort (monovariate analysis). The need to prescribe indomethacin in threshold ROP cases (55%) is significantly higher when compared to the total population in our unit (13%). The incidence of prescription of indomethacin in control infants (19%) is also slightly higher since mean birth weight and GA in controls are lower when compared to the total population (<1500 g, n= 571).

In contrast to the single report on dopamine and its associated risk to develop threshold ROP, the prescription of dopamine was not associated with an increased risk in this cohort[10]. This most likely reflects different therapeutic approaches between different NICUs.

Dopamine-induced vasoconstriction during early neonatal life may predispose to retinal ischaemia and result in greater release of vaso-proliferative factors, finally inducing more pronounced neo-vascularisation. Adrenergic receptors were identified in retinal vasculature and in retinal pericytes[16,17]. It is more likely that dopamine simply serves as a marker of symptomatic hypotension, and therefore is just another marker of disease severity. The observation that at least in this cohort, dopamine was no longer an independent risk factor after correction for any other marker of disease severity (CRIB, OI, MAP) is suggestive – but not conclusive – that the second explanation is more likely. A population based multi-centre study with specific emphasis on markers of disease severity and dopamine is the most appropriate way to solve this problem.

Similarly, the use of indomethacin served as a marker of PDA and was no longer an independent risk factor after correction for other markers of disease severity in this cohort. This clinical observation is in contrast with documented protective effects in animal studies[18]. In the TIPPI-trial, indomethacin prophylaxis in the first days of life had no effect on the incidence of retinopathy[19].

This is the first study to assess whether dopamine and/or indomethacin are independent risk factors to develop threshold ROP. We have shown that dopamine and indomethacin are indicators of an increased risk to develop threshold retinopathy but are no longer independent after correction of severity of disease. Since differences in management of hypotension or PDA between different NICUs exist, it may be more relevant to use more objective markers of disease severity (CRIB, OI) to further delineate the relative risk already associated with a given GA in order to develop a weighted risk score.

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