



Dopamine use is an indicator for the development of threshold retinopathy of prematurity

Michael B Mizoguchi, Thomas G Chu, Frederick M Murphy, et al.

Br J Ophthalmol 1999 83: 425-428

doi: 10.1136/bjo.83.4.425

Updated information and services can be found at:

<http://bjo.bmj.com/content/83/4/425.full.html>

These include:

References

This article cites 28 articles, 14 of which can be accessed free at:

<http://bjo.bmj.com/content/83/4/425.full.html#ref-list-1>

Article cited in:

<http://bjo.bmj.com/content/83/4/425.full.html#related-urls>

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic collections

Articles on similar topics can be found in the following collections

[Paediatrics](#) (353 articles)

[Retina](#) (1002 articles)

[Epidemiology](#) (4620 articles)

Notes

To order reprints of this article go to:

<http://bjo.bmj.com/cgi/reprintform>

To subscribe to *British Journal of Ophthalmology* go to:

<http://bjo.bmj.com/subscriptions>

Dopamine use is an indicator for the development of threshold retinopathy of prematurity

Michael B Mizoguchi, Thomas G Chu, Frederick M Murphy, Neil Willits, Lawrence S Morse

Abstract

Aim—To assess whether treatment of premature infants with dopamine is a risk factor for development of retinopathy of prematurity (ROP).

Methods—A retrospective case series analysis of two groups was utilised with a minimum follow up of 6 months. Clinical profiles and patient risk factors were identified along with an evaluation of ROP progression and an analysis of clinical outcome. All infants were seen in a single community neonatal intensive care unit (NICU). 41 consecutive high risk infants were identified during a 36 month period whose birth weight was less than 1000 grams and who remained in the NICU without transfer until at least 28 days of age. Dilated indirect ophthalmoscopy fundus examinations were performed on all infants to identify the degree of and progression to threshold ROP.

Results—18 of 41 infants were treated with dopamine for hypotension. The group of infants requiring dopamine differed statistically from the non-dopamine treated group by having a slightly higher birth weight, a greater incidence of hypotension and colloid treatment, and in manifesting more advanced respiratory disease. Within the dopamine treated group, 12 of 18 infants (67%) reached prethreshold ROP and seven infants (39%) reached threshold ROP requiring laser treatment. In contrast, only three of the infants (13%) who did not require dopamine for hypotension progressed to prethreshold ($p=0.001$) and only one of these infants (4%) progressed to threshold ROP ($p=0.02$). Logistic regression analysis among other variables demonstrated that dopamine use and gestational age are important factors in this low birthweight population for predicting the development of threshold ROP (dopamine use: adjusted odds ratio = 119.88, $p=0.0061$; gestational age: adjusted odds ratio = 0.061, $p=0.0043$).

Conclusions—Dopamine use in low birthweight infants may therefore be a risk factor for the development of threshold ROP. More vigilant screening of high risk infants requiring dopamine therapy for systemic hypotension may be warranted.

(*Br J Ophthalmol* 1999;83:425-428)

very low birthweight infants. As survival rates of premature low birthweight babies have increased, so the frequency of ROP has risen.¹⁻⁴ Initially, oxygen therapy was implicated in the aetiology of ROP⁵; however, it is now well recognised that ROP represents a multifactorial disease with numerous potential risk factors.⁶ Risk factors that have been reported include low birth weight, low gestational age, multiple gestation, prolonged parenteral nutrition, prolonged ventilator exposure, repeated blood transfusions, sepsis, apnoea, hypoxaemia, hypercarbia, and hypocarbia.⁶⁻¹⁰ The role of perinatal systemic complications and therapeutic interventions in the pathogenesis of ROP remains speculative. Systemic hypotension is a common complication of prematurity. Hypotension is often associated with other signs of low cardiac output, such as poor renal perfusion, decreased urine output and metabolic acidosis. It is usually initially treated with colloid, such as albumin, plasma, or other blood products. Dopamine, an α and β adrenergic agonist, is often administered to affected infants to counteract hypotension when they are unresponsive to volume expansion.^{11 12} We have recognised, with this subpopulation of high risk dopamine treated infants, an increased risk for the development of threshold ROP.

Methods

We performed a retrospective chart review of infants born in the neonatal intensive care unit (NICU) of the Doctors Medical Center (DMC) during a 36 month period beginning January 1991. Infants selected for study included those with a birth weight of 1000 grams or less (very low birthweight infants) and who remained in the NICU without transfer until at least 28 days of age. Two groups of infants were studied: a treatment group receiving dopamine and a control group not requiring dopamine. The two groups were compared with respect to birth weight, severity of ROP, dopamine treatment, gestational age, hypotension, colloid treatment for hypotension, intraventricular haemorrhage, sepsis, patent ductus arteriosus, indomethacin treatment, hyaline membrane disease, oxygen requirement, duration of ventilation, Apgar scores at 1 and 5 minutes, bronchopulmonary dysplasia, and dexamethasone treatment. The gestational age was determined from the last menstrual period until birth and revised when appropriate after postnatal examination. Hypotension was defined as a mean arterial pressure less than 30 mm Hg. Patients with hypotension

Department of
Ophthalmology,
University of
California at Davis,
Sacramento, CA, USA
M B Mizoguchi,
T G Chu
L S Morse

Department of
Statistics, University of
California at Davis,
Sacramento, CA, USA
N Willits

Department of
Pediatrics, Doctors
Medical Center,
Modesto, CA, USA
F M Murphy

Correspondence to:
Lawrence S Morse, MD,
Department of
Ophthalmology, University
of California at Davis, 4860
Y Street, Sacramento, CA
95817, USA.

Accepted for publication
30 September 1998

Retinopathy of prematurity (ROP) continues to be a significant cause of morbidity among

Table 1 Clinical characteristics for infants with birth weight ≤ 1000 g*

Clinical characteristics	Dopamine (n=18)	No dopamine (n=23)	Significance† (p value)
Birth weight (g)	868 (54)	816 (99)	0.03 WA
Gestational age (weeks)	26.3 (0.8)	26.8 (1.2)	0.14 WA
Hypotension	18/18 (100%)	11/23 (48%)	0.001
Colloid treatment	18/18 (100%)	10/23 (43%)	0.0004
Intraventricular haemorrhage	9/18 (50%)	6/23 (25%)	0.21
Sepsis	1/18 (6%)	1/23 (4%)	1.00
Patent ductus arteriosus (PDA)	10/18 (56%)	9/23 (39%)	0.46
Spontaneous closure of PDA	0/18 (0%)	2/23 (9%)	0.58
Indomethacin closure of PDA	9/18 (50%)	7/23 (30%)	0.34
Ligated PDA	1/18 (6%)	0/23 (0%)	0.90
Hyaline membrane disease	17/18 (94%)	13/23 (57%)	0.02
Oxygen requirement at day 2 (5)	34 (11)	27 (11)	0.02 MW
Days to first trial of extubation	17.4 (14.4)	9.8 (9.7)	0.02 MW
Apgar score at 1 minute	5.8 (2.3)	5.3 (2.9)	0.60 p(t)
Apgar score at 5 minutes	7.5 (1.5)	7.5 (2.4)	0.94 p(t)
Bronchopulmonary dysplasia	14/18 (78%)	16/23 (70%)	0.82
Dexamethasone treatment	13/18 (72%)	15/23 (65%)	0.89

*Values are mean (SD) for continuous data and number (%) of infants for categorical data. †WA = Welch-Aspin *t* test; MW = Mann-Whitney comparison; p(t)=Student's *t* test. χ^2 test with Yates's correction were used for categorical data.

were treated with dopamine only after treatment with colloid failed to elevate the mean arterial pressure above 30 mm Hg. Dopamine infusion was initiated at 5 μ g/kg/min with subsequent rates not exceeding 20 μ g/kg/min. In all cases, dopamine treatment was successful in elevating mean arterial blood pressure above 30 mm Hg. Clinical diagnosis of intraventricular haemorrhage was established by cranial ultrasonography. Sepsis was diagnosed by positive blood cultures at birth. Patent ductus arteriosus was confirmed by echocardiogram. Hyaline membrane disease was defined by an oxygen requirement greater than 30% at 48 hours and corroborated by chest *x* ray. Oxygen requirements were defined by the fraction of inspired oxygen at 48 hours. Duration of ventilation indicates the number of days of mechanical ventilation until the first trial of extubation. Bronchopulmonary dysplasia was defined by chest *x* ray criteria and oxygen requirement at 28 days. Dexamethasone treatment ranged from 1 to 6 weeks in duration.

Initial retinal examinations were performed between 4 and 8 weeks of age (mean 6 weeks). Each eye was graded using the standard international classification of ROP.¹³ Threshold ROP disease was also as defined in the Multi-center Trials of Cryotherapy for Retinopathy of Prematurity (CRYO-ROP).¹⁴⁻¹⁶ Infants with acute ROP were examined at 1-2 week intervals based upon the severity and progression of disease.

χ^2 with Yates's correction was used for categorical data. For contiguous data three

comparisons of analysis were performed and compared: a two tailed Student's *t* test which assumed equal variances in the groups, a Welch-Aspin *t* test that does not assume equal variances, and a non-parametric Mann-Whitney comparison. The choice of test reported in the tables is based on a test of equality of variances as well as whether the data for a given variable seemed to contain outliers. Logistic regression and stepwise logistic regression models were used to look at the joint impact of dopamine use, gestational age, birth weight, intraventricular haemorrhage, and oxygen requirement on the development of threshold ROP. These analyses were run using SAS PROC LOGISTIC (SAS Institute, Cary, NC, USA).

Results

Of 776 infants admitted to the DMC NICU from January 1991 to January 1993, 101 infants had a birth weight less than 1000 grams. Of these 101 infants, 25 died and another 23 neonates were transferred out of the NICU with 12 being transferred in before inclusion into this study, resulting in a total of 41 infants eligible for the study. The clinical data for those infants receiving dopamine (18 infants) and those not receiving dopamine (23 infants) are outlined in Table 1. Although there was a slight difference in age between the groups, infants in the non-dopamine treated group tended to be smaller than those later receiving dopamine treatment. This is probably due to the inclusion of infants with intrauterine growth retardation in the non-dopamine treated group. The data do, however, suggest that there are important differences between those infants ultimately requiring dopamine and those not. Important differences include hypotension, hyaline membrane disease, oxygen requirement at day 2, and the days to first trial of extubation. This suggests that there was greater respiratory distress in those infants ultimately receiving dopamine. As predicted, those requiring dopamine were also more unresponsive to colloid treatment and had greater hypotension.

Data from the group requiring dopamine and the group not requiring dopamine were compared with respect to degree and severity of ROP (Table 2). Of the 18 infants within the dopamine treated group, 12 infants (67%) reached prethreshold ROP and nine infants (50%) developed plus disease. In total, seven infants (39%) progressed to threshold ROP requiring treatment. By contrast, in the non-dopamine treated group, only three infants (13%) reached prethreshold ROP ($p = 0.001$), two infants (9%) developed plus disease ($p = 0.009$), and only one infant progressed to threshold ROP ($p = 0.02$). Table 3 demonstrates that infants who reached threshold ROP were significantly different from those which did not reach threshold ROP in that they had younger gestational age and had longer oxygen requirements, indicating more pulmonary disease.

A series of logistic regression models was used to look at the impact of dopamine use,

Table 2 Dopamine use and ROP classification for infants ≤ 1000 g

Clinical characteristics	Dopamine (n=18)	No dopamine (n=23)	Significance* (p value)
Infant ROP stage:			
No ROP	1 (6%)	4 (17%)	0.50
Any ROP	17 (94%)	21 (91%)	1.00
Prethreshold ROP	12 (67%)	3 (13%)	0.001
Plus disease	9 (50%)	2 (9%)	0.009
Threshold ROP	7 (39%)	1 (4%)	0.02
Anatomical zone on initial eye examination:			
Zone I	2 (11%)	3 (13%)	1.00
Zone II	14 (78%)	15 (65%)	0.60
Zone III	1 (6%)	5 (22%)	0.31

*p Values are based on χ^2 analysis with Yates's correction.

Table 3 Clinical characteristics for infants with ROP*

Clinical characteristics	Threshold ROP (n=8)	No threshold ROP (n=33)	Significance† (p value)
Hypotension	8 (100%)	21 (64%)	0.11
Colloid treatment	8 (100%)	20 (61%)	0.08
Hyaline membrane disease	8 (100%)	22 (67%)	0.14
Days to first trial of extubation	25.1 (12.3)	10.2 (10.8)	0.013 MW
Gestational age (weeks)	25.8 (0.8)	26.8 (1.2)	0.006 p(t)

*Values are mean (SD) for continuous data and number (%) of infants for categorical data.

†MW = Mann-Whitney comparison; p(t) = two tailed Student's *t* test. χ^2 with Yates's correction was used for analysis of categorical data.

gestational age, birth weight, intraventricular haemorrhage, and oxygen requirement on the development of threshold ROP. When all of these factors were included in the model, dopamine use (adjusted odds ratio = 119.88, $p = 0.0014$) and gestational age (odds = 0.061, $p = 0.0043$) were statistically significant, while the other three factors failed to be significant at the 0.05 level. The odds ratios indicate that dopamine use was positively associated with the development of threshold ROP. When a stepwise logistic regression was used, dopamine use (adjusted odds ratio = 30.70, $p = 0.032$) and gestational age (odds = 0.089, $p = 0.0013$) were still significant, while the other variables were not entered into the model.

The eight infants who developed threshold ROP all underwent indirect laser photocoagulation as previously described.^{17 18} All eyes of the treated infants remained anatomically attached at 6 months and had favourable outcomes.

Conclusion

ROP continues to be a significant cause of morbidity among very low birthweight infants. Effective treatment of ROP depends on the early and accurate recognition of those infants at highest risk for the development of ROP.

Low birthweight infants must contend with significant challenges for survival in the early perinatal period. A frequent challenge is the maintenance of cardiac output and systemic blood pressure. Despite intensive study of neonatal hypotension and its pharmacological management, an association with ROP has not been previously identified. Batton and coworkers found no difference between infants treated with cryotherapy and non-treated infants with regard to the presence of hypotension.¹⁹ Their definition of hypotension was any systemic blood pressure which required either volume replacement or inotropic medications; however, the use of dopamine was not specifically mentioned in their study. Moreover, Biglan *et al* reported similar blood pressure measurements in both their ROP and control patients.²⁰ Additionally, the CRYOROP study did not identify hypotension as a prognostic factor in the natural course of ROP.^{3 8}

We did, however, find a strong association between the development of threshold ROP characteristics and the use of dopamine therapy for hypotension in high risk infants with a birth weight of 1000 grams or less ($p = 0.02$, Table 2). Interestingly, one previous

study looked for an association between the use of dopamine therapy and the development of ROP.²¹ This study defined acute ROP as stage 1 disease or greater and did not find any association with dopamine use and the propensity to develop ROP. Because they did not try to relate their findings to threshold ROP, it is difficult to compare their findings with ours. In our study, 29 of the 41 infants were hypotensive. Hypotension was successfully treated in all 29 patients, with 10 of 41 infants responding to colloid treatment alone, and 18 of 41 infants responding to colloid plus dopamine treatment. Eight of the 29 infants went on to develop threshold ROP. None of the 12 non-hypotensive infants developed threshold ROP. Therefore, a direct measurement of the contribution of hypotension alone to the risk of developing threshold ROP cannot be estimated from our data.

In comparing our dopamine treated and non-treated groups, the two populations were statistically identical regarding other known risk factors for ROP such as gestational age,³ intraventricular haemorrhage,¹⁰ bronchopulmonary dysplasia,¹⁰ and dexamethasone treatment¹⁹ (Table 1). The degree of retinal maturation (Table 2) was also not significantly different in the dopamine treated infants when compared with the non-treated infants. Therefore, the degree of retinal maturation alone does not appear to have unfavourably predisposed the dopamine treated group to the development of threshold ROP.

To answer the question of what factors ultimately contributed to the greater likelihood of developing threshold ROP, we compared the clinical characteristics of those infants who developed threshold ROP with those infants who did not reach threshold ROP (Table 3). The data show that the two groups were different only with respect to the days to first trial of extubation and gestational age. This would suggest that there was greater respiratory distress among those who ultimately developed threshold ROP. Hypoxia has been associated with the development of ROP and those that developed ROP tend to be a more ill population of infants. Within the threshold ROP group, however, it is equally significant that 39% of the dopamine treated infants developed threshold ROP while only 4% of the non-dopamine treated group went on to develop advanced stages of ROP ($p = 0.013$, Table 2). A logistic regression analysis was performed to assess the impact of these and other variables and demonstrated that in this population of low birthweight infants, only dopamine use and gestational age are important factors for predicting the development of threshold ROP. When other potential predictors were assessed for threshold ROP, none was seen as significant. Lastly, even when we adjusted for the possible impact of those other variables, dopamine and gestational age are still seen as significant factors, with the estimates of the adjusted odds ratios coming out about the same in each of the models used.

Why dopamine use should predispose low birthweight infants to the development of

threshold ROP remains unknown and speculative. Dopamine is a potent inotropic agent with significant α and β adrenergic activity. Within the retina, α adrenergic receptors have been identified in retinal vasculature.²²⁻²⁴ Dopamine stimulation of these α adrenergic receptors could be postulated to result in retinal vasoconstriction. In infants receiving supplemental oxygen, dopamine use in the setting of neonatal hypotension may act synergistically with oxygen to further constrict retinal vasculature, resulting in an exacerbation of retinal ischaemia and the initiation of the development of ROP. Moreover, within the central nervous system, dopamine has been implicated in controlling the blood-brain barrier permeability.²⁵ Likewise, dopamine may also have a role in modulating the blood-retina barrier and the release of vasoproliferative factors in ROP. Dopamine has also been shown to play a primary role in retinal neuromodulation.²⁶ Dopamine metabolism within the retina has been correlated with eye growth and maturation.²⁷⁻²⁹ Administration of dopamine to premature infants may interfere with this normal maturation process and, therefore, may increase the risk of developing threshold ROP.

Our findings must be tempered somewhat by the realisation that dopamine use, itself may not be the sole factor responsible for the development of threshold disease, but rather may select for a sicker subpopulation of low birthweight infants at risk for the development of threshold ROP. Regardless of the underlying mechanism whereby dopamine may predispose low birthweight infants to the development of threshold ROP, dopamine use appears to have significant predictive value. Therefore, increased vigilance of screening in low birthweight dopamine treated infants appears warranted.

Presented in part at the Annual Meeting of the Association for Research in Vision and Ophthalmology, Sarasota, Florida, USA, 3 May 1993.

- 1 Gibson DL, Sheps SB, Schechter MT, et al. Retinopathy of prematurity: the new epidemic? *Pediatrics* 1989;**83**:486-92.
- 2 Gibson DL, Sheps SB, Uh SH, et al. Retinopathy of prematurity-induced blindness: birth weight-specific survival and the new epidemic [see comments]. *Pediatrics* 1990;**86**:405-12.
- 3 Palmer EA, Flynn JT, Hardy RJ, et al. Incidence and early course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Ophthalmology* 1991;**98**:1628-40.
- 4 Valentine PH, Jackson JC, Kalina RE, et al. Increased survival of low birth weight infants: impact on the incidence of retinopathy of prematurity. *Pediatrics* 1989;**84**:442-5.

- 5 Kinsey VE. Retrolental fibroplasia: cooperative study of retrolental fibroplasia and the use of oxygen. *Arch Ophthalmol* 1956;**56**:481.
- 6 Ben Sira I, Nissenkorn I, Kremer I. Retinopathy of prematurity. *Surv Ophthalmol* 1988;**33**:1-16.
- 7 Gunn TR, Easdown J, Outerbridge EW, et al. Risk factors in retrolental fibroplasia. *Pediatrics* 1980;**65**:1096-100.
- 8 Schaffer DB, Palmer EA, Plotsky DF, et al. Prognostic factors in the natural course of retinopathy of prematurity. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Ophthalmology* 1993;**100**:230-7.
- 9 Campbell PB, Bull MJ, Ellis FD, et al. Incidence of retinopathy in tertiary newborn intensive care unit. *Arch Ophthalmol* 1983;**101**:1686-8.
- 10 Brown DR, Biglan AW, Stretavsky MM. Retinopathy of prematurity: the relationship with intraventricular hemorrhage and bronchopulmonary dysplasia. *J Pediatr Ophthalmol Strabismus* 1990;**27**:268-71.
- 11 Padbury JF, Agata Y, Baylen BG, et al. Dopamine pharmacokinetics in critically ill newborn infants. *J Pediatrics* 1987;**110**:293-8.
- 12 Padbury JF, Agata Y, Baylen BG, et al. Pharmacokinetics of dopamine in critically ill newborn infants. *J Pediatrics* 1990;**117**:472-6.
- 13 Committee for the Classification of Retinopathy of Prematurity. An international classification of retinopathy of prematurity. *Arch Ophthalmol* 1984;**102**:1130-4.
- 14 Multicenter Trial of Cryotherapy for Retinopathy of Prematurity. Preliminary results. Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Arch Ophthalmol* 1988;**106**:471-9.
- 15 Multicenter Trial of Cryotherapy for Retinopathy of Prematurity. One-year outcome—structure and function. Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Arch Ophthalmol* 1990;**108**:1408-16.
- 16 Multicenter Trial of Cryotherapy for Retinopathy of Prematurity. Three-month outcome. Cryotherapy for Retinopathy of Prematurity Cooperative Group. *Arch Ophthalmol* 1990;**108**:195-204.
- 17 Benner JD, Morse LS, Hay A, et al. A comparison of argon and diode photocoagulation combined with supplemental oxygen for the treatment of retinopathy of prematurity. *Retina* 1993;**13**:222-9.
- 18 Landers MB, Toth CA, Semple HC, et al. Treatment of retinopathy of prematurity with argon laser photocoagulation. *Arch Ophthalmol* 1992;**110**:44-7.
- 19 Batton DG, Roberts C, Trese M, et al. Severe retinopathy of prematurity and steroid exposure. *Pediatrics* 1992;**90**:534-6.
- 20 Biglan AW, Cheng KP, Brown DR. Update on retinopathy of prematurity. *Int Ophthalmol Clin* 1989;**29**:2-9.
- 21 Hammer ME, Mullen PW, Ferguson JG, et al. Logistic analysis of risk factors in acute retinopathy of prematurity. *Am J Ophthalmol* 1986;**102**:1-6.
- 22 Nielsen PJ, Nyborg NC. Adrenergic responses in isolated bovine retinal resistance arteries. *Int Ophthalmol* 1989;**13**:103-7.
- 23 Ferrari-Dileo G, Davis EB, Anderson DR. Response of retinal vasculature to phenylephrine. *Invest Ophthalmol Vis Sci* 1990;**31**:1181-2.
- 24 Ferrari-Dileo G, Davis EB, Anderson DR. Effects of cholinergic and adrenergic agonists on adenylate cyclase activity of retinal microvascular pericytes in culture. *Invest Ophthalmol Vis Sci* 1992;**33**:42-47.
- 25 Palmer GC. Neurochemical coupled actions of transmitters in the microvasculature of the brain. *Neurosci Biobehav Rev* 1986;**10**:79-101.
- 26 Dowling JE. Retinal neuromodulation: the role of dopamine. *Vis Neurosci* 1991;**7**:87-97.
- 27 Laties AM, Stone RA. Some visual and neurochemical correlates of refractive development. *Vis Neurosci* 1991;**7**:125-8.
- 28 Stone RA, Lin T, Laties AM, et al. Retinal dopamine and form-deprivation myopia. *Proc Natl Acad Sci USA* 1989;**86**:704-6.
- 29 Stone RA, Lin T, Iuvone PM, et al. Postnatal control of ocular growth: dopaminergic mechanisms. *Ciba Found Symp* 1990;**155**:45-57.