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Controlled trial of D-penicillamine to prevent retinopathy of prematurity

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204 infants with birthweights between 751 and 2000 g and 26—35 weeks gestational age (100 treated and 104 control subjects) were enrolled in a prospective controlled trial of the effectiveness of D-penicillamine (DPA) in the prevention of retinopathy of prematurity (ROP). The two groups did not differ significantly in gestational age, birth weight, Apgar scores, the time of exposure to oxygen and in the incidence of PDA or in the number of exchange transfusions and *RBTs*.

Of the treated infants 29, and of the control infants 34 died before the tenth week of life. These cases were not included in further analysis. Patients were subsequently examined and assessed by two ophthalmologists independently, who did not know which babies were receiving DPA. Six of the 70 surviving control infants and none of the 71 surviving treated infants had ROP stage II or graver.

The results suggested that ROP may effectively be prevented with DPA in very low-birth-weight-infants, and that the drug has no serious adverse effects during the neonatal period.

Although retinopathy of prematurity (ROP) or, according to the traditional term, retrolental fibroplasia (RLF) had been described more than 40 years ago [53], it remains an unsolved problem [1, 20, 21, 30, 38, 39, 40, 47, 48]. Cases of ROP still occur today despite improvements in monitoring oxygen therapy [3, 12, 49, 52, 55] and using high preventive doses of vitamin E [14, 18, 19, 22, 29] in the intensive care nursery. The increased survival rate among extremely low-birth-weight infants, combined with additional factors other than excess oxygen, may be responsible for the "second epidemic" of the disease [4, 10, 15, 13, 26, 31, 46].

In our department we have used D-penicillamine (DPA) for the treatment of neonatal hyperbilirubinaemia since 1973 [27, 28]. We have recently reported that DPA therapy in the neonatal period is associated with a marked decrease in the incidence of severe RLF among very-low-birth weight infants [24, 25, 26].

The history of DPA in preventing RLF can be divided into three periods in our department (see Table I). *In the first period* we administered DPA only against hyperbilirubinaemia as indicated in Table I. The original aim of our retrospective screening programme, carried out in the spring of 1979, was to estimate the incidence of RLF during the period 1974—1978. It was surprising that among babies treated with DPA to prevent hyperbilirubinaemia there

TABLE I

The history of D-penicillamine treatment of < 1500 g birthweight neonates in Debrecen, Hungary

	First period (1974—78)	Second period (1979—80)	Third period (1981—82)
Dosage and application	300 mg/kg IV for 3 days	300 mg/kg IV for 3 days	300 mg/kg IV for 3 days + 50 mg/kg IV for 2 weeks
Number of survivals	193	133	152
DPA-treated	61	133	152
RLF	1	1	1
Untreated	132	—	—
RLF	10	—	—

was only one case of RLF, whereas ten out of the 132 babies without such treatment developed severe cicatricial stages of the disease. We then decided that all infants of less than 1500 g birthweight and requiring supplemental oxygen should receive DPA therapy.

During the second period (1979—1980) of DPA treatment there was one case out of 133 surviving infants who developed RLF. This baby received DPA for three days and oxygen therapy for three weeks. We then changed the dosage and duration of DPA administration.

During the third period (1981—1982) a new mode of DPA application was introduced in January. It was, however, still not able to totally eradicate the *occurrence* of RLF, as shown by the data in Table I.

We believe that the above clinical observations provided support for conducting a strictly controlled prospective trial [41] to investigate the prevention of the cicatricial form of the disease (RLF) and the reduction of its acute stage (ROP).

PATIENTS AND METHODS

Subjects

The Newborn Intensive Care Unit (NICU) of the University Medical School, Debrecen, Hungary, is a centre for critically ill newborns. All our patients are born elsewhere but are transferred by ambulance to our Department in the first 24 hours of life. The present study included infants who had been born between January 1, 1983, and March 6, 1984, and had a birthweight between 751 and 2000 g. Gestational age was determined by maternal data and Dubowitz assessment [11].

The infants were nursed in incubators. All prematures had received oxygen therapy for hyaline membrane disease, congenital pneumonia, recurrent apnoea, wet lung, congestive heart failure, aspiration syndrome, or CNS lesion. The infants received uniform care after admission to the NICU. Oxygen therapy was administered by hood, nasal prongs, endotracheal tube, or CPAP ventilation at concentrations sufficient to maintain arterial oxygen tension between 50 and 70 mm Hg. An umbili-

cal-artery catheter was inserted in all infants requiring FiO_2 greater than 0.6, or mechanical ventilation, so that arterial blood gases could be determined. When possible, PaO_2 was continuously monitored by means of transcutaneous (TC)PO_2 electrodes (Radiometer, Copenhagen, Denmark), for intermittent periods. The haematocrit of acutely ill babies was kept under 55% by partial exchange transfusion with fresh frozen plasma. Double volume exchange tranfusion was performed when indicated for either hyperbilirubinaemia or sepsis. The indications of replacement blood transfusion (RBT) were severe anaemia and sepsis, or other conditions requiring prolonged oxygen therapy.

Study design

204 preterm babies of 26—35 weeks gestational age were enrolled in the study. Informed consent was obtained from the parents and the trial was approved by the ethical committee of the University. Reasons for non-enrolment were a significant congenital abnormality in 14 babies, or death before 6 hours of life in 6 babies.

Infants in the study were randomly allocated to control and treatment groups by means of sealed envelopes according to birthweight (751—1000 g, 1001—1250 g, 1251—1500 g, 1501—1750 g, 1751—2000 g).

Infants in the treated group were given daily 3 doses of 100 mg/kg body weight DPA (Metalcaptase^R — Knoll AG, Ludwigshafen, FRG) intravenously (IV) for 3 days. The first dose was administered within 12 hours of birth. Babies below 1500 g continued to receive DPA once daily in a dose of 50 mg/kg body weight IV till the end of the second week of life. Infants above 1500 g were treated with DPA beyond 3 days only in cases where prolonged oxygen therapy was necessary. — We were unable to measure the serum level of DPA in the treated group. No placebo was given to control subjects. Haematocrit, haemoglobin, WBC, platelet count, electrolytes, blood gases, bilirubin, phototherapy and urine analysis were recorded regularly until discharge.

Ophthalmological examination

Examinations were conducted weekly at a set time to ensure regularity of visits to the premature nursery. The infants were first seen by an ophthalmologist (I.H.) at 6 weeks of age. He did not know which babies had received DPA. The pupils were maximally dilated with a mixture of phenylephrine and cyclopentolate. Ocular examination was performed with an indirect (Keeler) ophthalmoscope without scleral depression. Any infant who showed evidence of ROP had regular ophthalmological examination until discharge. Abnormalities were noted and fundus drawings were made. All infants were reassessed before discharge from the NICU. The findings in the acute phase of retinopathy were recorded on basis of the new international classification of ROP [2, 36]. Grading of the cicatricial phase was according to the classification of Reese et al. [44]. The babies were subsequently examined and assessed by an independent ophthalmologist (É.K.) unaware of the previous therapy. The last ocular examination was performed at the age of 6 months.

Statistical analysis

Clinical details were recorded by computer. Comparison between DPA and control groups with respect to baseline characteristics and outcome was carried out using Student's test, Chi square test, Mann—Whitney U and Fischer's exact tests. For all analyses, $p = 0.05$ was taken as the criterion of statistical significance.

Results

Of the infants, 63 died before 10 weeks of age and were not evaluated for the presence of ROP. 141 babies completed the trial; 71 in the DPA group and 70 in the control group.

Infants enrolled in the study are shown in Table II, according to their

TABLE II

Infants enrolled in the study

Birthweight, g	DPA		Control	
	All/survived (per cent)			
751—1000	12/4	(33.3)	10/1	(10.1)
1001—1250	19/11	(57.9)	21/13	(61.9)
1251—1500	35/28	(80.0)	37/26	(70.3)
1501—1750	19/15	(78.9)	23/19	(82.6)
1751—2000	15/13	(86.7)	13/11	(84.6)
Total	100/71	(71.0)	104/70	(67.3)

TABLE III

Baseline characteristics of the study population

	DPA	Control
No of infants	71	70
<1500 g birthweight	43	40
Gestational age, weeks, mean (SD)		
Overall	31.8(2.0)	31.5(2.3)
<1500 g birthweight	30.2(2.0)	30.7(2.4)
Birthweight, g, mean (SD)		
Overall	1488(281)	1474(246)
1500 g birthweight	1299(165)	1310(154)
Male/female	34/37	30/40
Apgar score 1 min. Median (range)	5(1—9)	6(1—9)
Apgar score 5 min. Median (range)	7(3—9)	7(4—9)
Transported from distance of		
<10 km	39	38
10—120 km	32	32
No of infants		
Singletons	59	60
Twins	10	9
Triplets	2	1
Birthweight <10th centile for gestational age	11	13
Delivered by Caesarean section	15	12
Received antenatal dexamethasone	35	38
Received phototherapy	62	68
Received exchange transfusion	15	18
Received RBT	53	50
With severe acidosis (pH <7.2)	31	30
With severe hypercarbia ($paCO_2$ >50 mm Hg)	35	36
With episodes of hyperoxia (paO_2 >100 mm Hg)	21	19
With episodes of hypoxia (paO_2 <40 mm Hg)	33	35
With hyperviscosity	19	18
With sepsis	7	9
With PDA (clinical)	7	7
With haemorrhagic tendency	16	12
Median (range) duration of oxygen treatment (h)	128(27—898)	125(21—860)

birthweight. Table III demonstrates the baseline characteristics of the study population. There were no significant differences between the two study groups in mean birthweight, gestational age, Apgar scores, or with respect to the most important perinatal data which are considered risk factors for ROP and RLF. The two groups did not differ significantly in the duration of oxygen exposure and in the incidence of patent ductus arteriosus (PDA) treated with indomethacin, or in the number of RBT. Only one case of bronchopulmonary dysplasia developed in the control infants. The very low incidence of this disorder among our patients was explained by the fact that only few cases survived long-term mechanical ventilation. Most of the infants were treated with nasal or orotracheal CPAP or oxygen delivered via head hood. No statistically significant difference could be found in the treatment delivered to DPA-treated prematures when compared to controll infants. Exposure to very high ambient oxygen tensions (FiO_2: 0.8—1.0) beyond 48 hours of age was uncommon in both groups.

During the 14 months study period, 6 infants were diagnosed as having ROP stage II or graver during their hospital stay. Both eyes were affected equally. All of these prematures belonged to the control group, so with respect to the frequency of the active phase of the disease, the difference between the DPA treated and the control group was significant statistically ($p = 0.013$) using Fischer's exact test. DPA was found to reduce the incidence of ROP significantly not only in the overall study population but in the infants of less than 1500 g birthweight (DPA: 43/0 *vs* control: 40/6; $p = 0.010$). Table IV reveals that ROP occurred exclusively in neonates with birthweights 1001 to 1500 g. Table IV also shows the most severe stage of ROP according to the

TABLE IV

Frequency of retinopathy of prematurity in the study population

Study population	Normal	Stage of the disease*			
		1	2	3	4
DPA group	71				
Control group					
751—1000	1				
1001—1250	8		2	1	2
1251—1500	25			1	
1501—1750	19				
1751—2000	11				

* Stage 1 — Demarcation line
Stage 2 — Ridge
Stage 3 — Ridge with extraretinal fibrovascular proliferation
Stage 4 — Retinal detachment

new international classification. Infants with ROP had a gestational age ranging from 27 to 31 weeks. It has to be noted that the duration of oxygen therapy in the cases with ROP did not differ significantly from that of the overall study population. All but one had double volume exchange transfusion.

Any infant found to have ROP, whatever its stage, was removed from the study and treated with DPA in a dose of 50 mg/kg bodyweight IV daily for three weeks, and also cryopexy, if it was indicated. The outcome of ROP cases was as follows: 2 infants with stage II and III recovered completely, 3 babies with stage II, III and IV, respectively, developed grade I cicatricial phase, with relatively good vision. Only one case of stage IV developed grade II RLF.

No blindness occurred during the study period.

Discussion

We uphold the view stated by Lucey and Dangman [31]: ". . . RLF is an extremely difficult disease to prevent, treat, or investigate. A disease of this complexity with multiple causes will require very large numbers of infants in any controlled study of a therapy." This sample size, however, would be impractical for any single institution. Our aim was to use the smallest possible sample size yet large enough to have a reasonable chance of detecting any clinically important benefit of the investigated treatment. The number of patients to be included in the study was calculated in advance to be 66 in the control and treated groups, respectively. This assumption was based on an expected ROP rate of 8—10% in infants under 2000 g birth weight [5, 9, 42, 50, 55] and a calculated reduction in frequency of ROP to less than, or equivalent to, 1% in the DPA-treated group ($p_1 = 0.08$; $p_2 = 0.01$; $z = 1.96$) [13]. The likelihood of erroneously rejecting the null hypothesis that the prophylactic administration of DPA had no effect on the incidence of ROP in our patients, was less than 5% with 95% confidence. Thus, the Type I (alpha) error was at the $P = 0.05$ level in our study. After completion of the study, the sample size had a power of 73% for detecting a worthwhile treatment difference if the rate of ROP frequency for the treatment and control groups were 0% and 8.6%, respectively. Thus the Type II (beta) error was at the $P = 0.27$ level. This suggested to accept the hypothesis that DPA protects the eyes of infants against ROP.

When ROP was diagnosed in six infants we completed the blind controlled trial of DPA prophylaxis. Following this the six appeared to have been enrolled in an uncontrolled trial of the effect of DPA plus cryotherapy in progressing ROP. We must make it clear, however, that the latter trial is quite separate from the prophylaxis trial and that the latter results are based on a very small number of patients and have not passed a rigorous test.

How does D-penicillamine act against retinopathy of prematurity?

The aetiology of ROP is now accepted as multifactorial [4, 5, 10, 15, 16, 23, 31, 35, 46]. It may be assumed that the development of ROP is triggered by a number of conditions which may disturb the retinal circulation and result in ischaemic retinopathy with the consequence of vasoproliferation and cicatrisation. Of these factors, the immaturity and the oxygen toxicity, which latter is not equivalent to supplemental oxygen therapy [33], are considered to be the most important.

According to our hypothesis [7, 25, 29, 32, 33, 34], DPA appears to have several modes of action against ROP. The drug scavanges oxygen-free radicals [51] produced by hyperoxia, hypoxia [45] or other conditions frequent in very low-birthweight, sick prematures. In addition, this chelating agent facilitates heme synthesis and inhibits heme degradation in newborn animals. As those enzymes that play an important role in antioxidant defense (peroxidases, catalase) are heme proteins, it is reasonable to conclude that in preventing hyperbilirubinaemia and ROP the mechanism of action of DPA may be identical: the protection of biomembranes against lipid peroxidation. — DPA as a collagen antagonist [8, 37, 43] causes an increase in soluble collagen in soft tissues; intramolecular cross-linkages are blocked, and an absence of intramolecular covalent bonds has been shown. The formation of fresh insoluble collagen is nearly quantitatively inhibited. Furthermore, DPA accelerates the turnover of preexisting insoluble collagen by cleaving intermolecular bonds. Of even more concern is the effect of DPA on the solubility of vitreous collagen [6]. In animals treated with DPA it was found that 47% of the vitreous collagen became soluble after treatment with DPA, compared with 6% in the control group. This observation was confirmed by another experimental study which demonstrated that DPA reduced vitreous proliferation after perforating injury [54]. Consequently, the inhibitory effect of DPA on collagen synthesis may be beneficial also in the process characterized by neovascular proliferation and cicatrisation.

Safety and tolerance of D-penicillamine

In the last eleven years we have given high doses of DPA for some days to more than 3000 term and preterm infants, observing neither acute nor long-term adverse effects nor any late complication during several years follow-up. In spite of this, paediatricians seem reluctant to use DPA in newborn babies probably because long-term administration of the drug in rheumatic arthritis was often followed by unpleasant and dangerous side effects [17].

In our recent controlled trial, DPA therapy was well tolerated by all study infants. No single DPA treated premature was withdrawn because of severe side effects. Mortality rates in the two groups were similar (see

Table II). Including patients who died beyond 10 weeks of age, the rates were 31% and 33.7% for the DPA-treated and the control babies, respectively. There were no significant differences when the data were analysed by cause of death and complications of intensive care. No rash, thrombocytopenia, agranulocytosis, albuminuria and myasthenia, frequently encountered in adults, were observed during the study period. There were no significant differences in treated and control groups with respect to initial weight loss and subsequent weight gain, or weight gain and head circumference corresponding to the six-month adjusted age.

In summary, our results suggest that ROP could effectively be prevented with DPA in very low-birth-weight-infants, and that the drug has no serious adverse effects during the neonatal period. It would be desirable to conduct further collaborative studies by several investigators to recruit large numbers of patients in order to therapeutic effectiveness.

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Addendum

After completion of this manuscript a new case of RLF was diagnosed at our Follow-up Clinic. This infant of 28 weeks gestational age had a birthweight of 850 g. She was born after termination of the trial and so was not enrolled in the study. DPA was administered daily until the 7th day when it had to be withdrawn owing to haematuria which developed in association with sepsis and DIC. She received an exchange transfusion and subsequently RBTs 3 times. At the age of 12 weeks routine ophthalmological examination revealed no change in the eyes. She had then a weight of 1600 g and was returned to the county hospital from where she had initially been referred to us. We lost sight of her until her first visit to our Follow-up Clinic at the age of 6 months. The ophthalmologist diagnosed a severe cicatricial phase of ROP in both eyes.

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