

One year longitudinal follow-up of premature infants treated with D-penicillamine in the neonatal period

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A prospective controlled trial has recently been reported to show the effectiveness of D-penicillamine (DPA) in the prevention of retinopathy of prematurity (ROP) among infants less than 2000 g birth-weight. The present paper is a comprehensive overview of a cohort of 204 prematures enrolled in the above study, with respect to mortality and outcome.

Survival rate in the DPA treated group was the same as of those receiving conventional therapy. When the outcome of the DPA treated and the control infants was compared in terms of both major and minor impairments, the frequency of disabled and handicapped infants was higher in the control group. The same was observed with respect to the number of repeated hospital treatments, which was significantly higher among the control babies.

The results suggest that DPA effectively prevents ROP among very-low-birth-weight infants, and also that the drug has no adverse effect on either mortality or late development.

In spite of all the technical advances facilitating continuous monitoring of vital functions in intensive care nurseries which are suitable to diminish mortality among low-birth-weight (LBW) infants, some chronic conditions of immature babies, such as retrolental fibroplasia (RLF) or bronchopulmonary dysplasia (BPD) remain unsolved problems.

We have recently reported a prospective controlled trial about the effectiveness of D-penicillamine (DPA) in the prevention of retinopathy of prematurity (ROP) [9]. Six of the surviving 70 control infants and none of the 71 surviving DPA treated infants had ROP stage II or worse.

When considering the benefits of a new drug, it is important to measure

its potential side effects. Still, to judge adverse effects among LBW infants is a difficult task. These babies are obviously at high risk for a variety of factors and they are subjected to many therapeutic interventions which may be more dangerous than DPA treatment. It should be remembered that determination of the risk/benefit ratio does not arise in connection with a given disease in neonatal intensive care but presents itself in relation to two crucial questions: the mortality rate on the one hand and the outcome on the other.

As far as the outcome is concerned, not only the conventional method of evaluation was considered by reporting the rates of major neurological, developmental and other handicaps,

but a broader spectrum of developmental morbidity (rehospitalization, physical growth and minor neurological and perceptual abnormalities) were also taken into account [6, 14]. This report represents a comprehensive overview in the first year of life incorporating all the above factors, from a cohort on infants enrolled in the above mentioned prospective study.

PATIENTS AND METHODS

The prospective controlled trial of DPA to prevent retinopathy of prematurity was carried out in the Neonatal Intensive Care Unit, between the January 1st, 1983, and March 6th 1984. 204 infants with birth-weight between 751 and 2000 g and 26–35 weeks of gestational age (100 treated and 104 control subjects) were enrolled in the study. Details of the study have recently been published [9]

Follow-up examinations

Parents were introduced to the follow-up program prior to the infants' discharge from the nursery, which normally occurred when they weighed at least 2400 g, were in room air and were fed orally. This generally took place between 39 and 44 weeks of corrected or postmenstrual age. As a rule, infants with chronic complications required longer hospitalization. After discharge, infants were followed prospectively at the corrected age of at least 1, 3, 6 and 12 months. They were evaluated for growth, physical, developmental and neurological status, hearing and vision. Neurological examination was carried out by a modified method of Vojtá [15], development was measured by Brunet-Lesine's test [2] which has been standardized for the Hungarian population, and the achievement of the child is taken as normal over

70 points. Interim medical history was invariably documented. Social background was evaluated in terms of a modified version of Graffar's index [4]. Both in the DPA treated and the control group the rate of children living in poor conditions was higher (24% and 30%, respectively) than the figure for the general population. Only a quarter of the infants in either group had a better socioeconomic background with at least one parent having graduated from college and having a well-paid job. The follow-up staff was unaware whether a baby belonged to the DPA treated or the control group.

In the study period 137 infants were discharged from the nursery. Complete follow-up information permitting valid conclusions to be drawn was obtained for 120 children (87.5%), sixty in each group. 17 children (eight in the DPA treated and nine in the control group) were lost for follow-up. Three moved to other areas of the country and the rest failed to attend all or most of the follow-up examinations. According to the information obtained from the district pediatricians and local health service none of the latter suffer from serious developmental delay or chronic illness.

Statistical analysis

Comparison between the DPA treated and the control group with respect to mortality and outcome was carried out using Student's test, chi square test, Mann-Whitney U and Fischer's exact tests; in all evaluations $p < 0.05$ was taken as the criterion of statistical significance.

RESULTS

Mortality

Overall mortality of the study population was 32.3%, 31% in the DPA treated, and 33.7% in the control group. (Table I). There was no signi-

ficant difference between the two groups either in overall or in birth-weight specific mortality rate.

Survival rate of the very low birth-weight (VLBW) infants was 61.7%, 65.1% in the DPA treated, and 58.8% in the control group, which corresponds to the survival rates of the late 1970s but was higher than in the early 1980s [3, 7, 8, 12]. Comparison of survival rates between hospitals is difficult because of possible differences in populations (frequency of outborns, variable socioeconomic conditions, etc.), the philosophy of perinatal care and its technique. The higher

mortality rate of our study populations was probably due the fact that all our infants were outborn and the level of primary care varied greatly in the seven obstetric hospitals which had referred the babies to us. The main causes of death of all the 66 infants are summarized in Table II. In both groups, haemorrhagic complications were dominant, intraventricular haemorrhage in particular. The next major cause was infection. In sum, the group of infants treated with PDA in the neonatal period showed the same mortality figures as those subjected to the usual therapy.

TABLE I
Mortality of infants

	Number (per cent)	
	DPA treated (n = 100)	Control (n = 104)
All deaths	31 (31)	35 (33.7)
Early neonatal deaths (0-6 days)	15 (15)	17 (16.3)
Late neonatal deaths (7-27 days)	14 (14)	15 (14.4)
Infant deaths	2 (2)	3 (2.9)

TABLE II
Causes of death in study population

	Number	
	DPA treated (n = 31)	Control (n = 35)
Pneumonia	3	2
Bronchopulmonary dysplasia	—	1
Pulmonary haemorrhage	4	5
Intraventricular haemorrhage	18	21
Sepsis	3	4
Meningitis	2	1
Hydrocephalus	1	—
SIDS	—	1

OUTCOME AT 1 YEAR OF CORRECTED
AGE

Neurological outcome

One hundred and six babies (88.3%) of the study population were neurologically normal at follow-up (Table III.). Six (5%) had minor problems of motor overactivity or muscle tone deviation. Eight (7%) of the children were neurologically abnormal, three in the DPA treated and five in the control group. One child suffered from epilepsy and seven had cerebral palsy. There was hardly any difference in the number of children suffering from cerebral palsy between the two groups, but there was in the severity of their impairment. While in the DPA treated group there were only three mild cases of spasticity (all functioning normally, DQ 81, 81 and 94, respectively), in the control group there were two children with

mild spastic diplegia and hemiparesis (DQ 90 and 88, respectively), the other two suffered from moderate (DQ 76) and severe tetraspasticity, the latter with profound mental and motor handicap associated with microcephaly.

Developmental outcome

With the exception of three babies in the VLBW category, the patients' developmental functioning was within normal limits at 1 year of corrected age. One child in the control group was too severely handicapped for quantitative psychometric testing (Table IV), but concerning their real age, 14 of the 119 patients showed a developmental delay. Infants in the higher birth-weight category had better performance figures than those belonging to the VLBW category. Among the latter the mean DQ was just over the normal limit in both groups. The

TABLE III
Neurological outcome at 1 year of corrected age

Birth weight category	<1500 g		1501—2000 g	
	DPA (n = 36)	Control (n = 36)	DPA (n = 24)	Control (n = 24)
Minor neurological problems	2	2	1	1
Epilepsy	—	1	—	—
Cerebral palsy	3	3	—	1
	↓	↓		↓
	Spastic diplegia mild	Spastic diplegia mild		Spastic tetraparesis severe (microcephaly)
	Spastic diplegia mild	Spastic hemiparesis mild		
	Spastic hemiparesis mild	Spastic tetraparesis moderate		

TABLE IV
Developmental outcome at 1 year of corrected age

	<1500 g		1501-2000 g	
	DPA (n = 26)	Control (n = 36)	DPA (n = 24)	Control (n = 23+1*)
Corrected				
age DQ (mean)	86.4 ± 13.5	88.4 ± 13.9	92.3 ± 11.3	90.9 ± 12.8
DQ < 70 (n)	1	2	—	1*
Real age DQ (mean)	74.8 ± 11.2	78.8 ± 13.9	83.7 ± 9.8	81.5 ± 11.0
DQ < 70 (n)	5	5	1	3+1*

differences between the DPA treated and control infants were not significant.

Ophthalmological outcome

Substantial differences were found between the DPA treated and the control group among the VLBW infants not only in the frequency of ROP but also with respect to other ophthalmological disturbances. Whereas in the DPA treated group there were only two children who had any visual abnormality (one of them needed correction of vision), in the control group 25% of the children suffered from various ophthalmological disturbances disturbing their normal functioning. In addition to the four RLF children (two of them having other visual lesions, too) four other infants suffering from amblyopia or myopia needed correction of vision.

In the higher birth-weight category the visual abnormalities were not so striking: in the DPA treated group four had strabismus while in the control group two had myopia and two strabismus.

Physical growth

Table V. shows the mean weights, lengths and head circumferences of the study population in the two different birth-weight categories at 12 months of corrected age. The overall picture of somatic development seemed to be somewhat more favourable in both birth-weight categories in the DPA treated group, but the differences were not significant statistically. At that age about 10% of the infants in the higher, and about 50% in the lower birth-weight category were two standard deviations below the mean in height and/or weight according to the growth chart of Babson [1].

TABLE V
Somatic development at 12 months of corrected age

Study group	DPA treated		Control		
	Birth-weight category		Birth-weight category		
Somatic development	<1500 g (n = 36)	1501-200 g (n = 24)	<1500 g (n = 36)	1501-2000 g (n = 24)	
Weight, g mean	8199	±1256 9389	±1653 7942	±1230 9181	±1288
Length, cm mean	71.0	±3.9 73.8	±4.2 70.6	±4.0 73.2	±4.1
Head circumference, cm mean	44.8	±1.74 45.9	±2.0 44.6	±1.8 45.2	±1.6

Rehospitalization

A proper measure of subsequent morbidity relates to the incidence and causes of rehospitalization. These two factors evaluated in the period between discharge from the nursery and the corrected age of one year. With respect to the need for hospital treatment, in both birth-weight categories the control infants showed a considerably larger figure for the number of patients and the number of readmissions than did the DPA treated babies (Fig. 1). In the DPA treated group,

with the exception of one child who was admitted three times, all rehospitalized infants required hospital care only once or twice. Only children belonging to the control group were rehospitalized as many as five or six times. Respiratory tract infections constituted the major cause of the repeated hospital treatment in both groups, which was in agreement with the data of other authors [5, 6, 10] (Table VI).

Thus 15 children, one fourth of the DPA treated group, were rehospitalized on 23 occasions, which means an

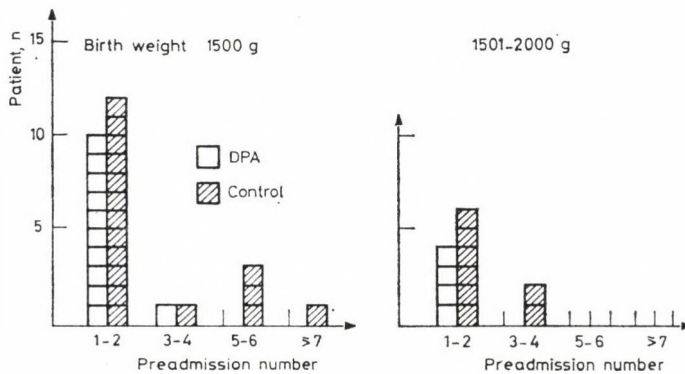


FIG. 1. Frequency of rehospitalisation

TABLE VI
Causes of rehospitalisation

Causes	DPA	Control
	Children (admission)	
Respiratory tract infection	12 (20) ^a	17 (45) ^a
Convulsion	2 (2)	2 (2)
Urinary tract infection	1 (1)	4 (4)
Other causes	—	5 (8)
Total	15 ^b (23) ^c	28 ^b (59) ^c

^a $p < 0.001$

^b $p < 0.05$

^c $p < 0.001$

admission ratio of 1.58 per child. As opposed to this, in the control group twice as many children needed hospital treatment, on 59 occasions in all, which means a ratio of more than two admissions per child. The statistical significance observed should be obvious from Table VI. A possible explanation for these differences may be the beneficial effect of DPA treatment in the early neonatal period on maturation of the immunological system of prematures. Furthermore, like the other chelating agents, DPA is likely to have an antiviral effect.

DISCUSSION

In the last 13 years we have given high doses of DPA for some days to more than 3500 term and preterm infants observing neither acute nor long-term adverse effects nor any late complications 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 [9]. In the recent trial, the drug was tolerated well by all the 100 LBW babies.

The survival rate in the DPA treated group was the same as among those who received the conventional therapy. DPA did not alter the mortality spectrum either in any birth-weight category or with respect to the most possible causes of death.

The rate of survival is only one measure of the efficacy of perinatal care. The other very important question is the quality of survival which is significantly harder to measure, and years may elapse before the full impact of a new technology or treatment modality on outcome becomes apparent [7].

Short-term (one or two years) follow-up results of the late 1970s and the early 1980s documented that the frequency of major handicaps (cerebral palsy, mental developmental delay, epilepsy, hydrocephalus, deafness

and blindness) varied between 8 and 19% among the VLBW infants [8, 11, 12]. In the recent trial the frequency of major impairments among the VLBW infants was 19.4%, but 10 of the 14 impaired children have tolerable functions (one with epilepsy, five with a mild degree of cerebral palsy and the four RLF children, since none of them went blind) and only the remaining four infants should be considered to be handicapped. When the outcome of DPA treated and the control infants is compared in terms of both major and minor impairments, the frequency of disabled and handicapped infants was higher in the control group than among the DPA treated babies. The same was observed with respect to the number of repeated hospital treatments, which was significantly higher among the control babies.

In sum, our results suggest that not only ROP and RLF could effectively be prevented with DPA administration among the VLBW infants, but also prove that the DPA has no serious adverse effects on later development.

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