

Pyritinol for Post-asphyxial Encephalopathy in Term Babies – *A Randomized Double-Blind Controlled Trial*

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Objective: To evaluate the efficacy of pyritinol in improving the neurodevelopmental outcome at one year of age among term babies with post-asphyxial encephalopathy.

Setting: Level II Neonatal Nursery and Child Development Centre, Medical College, Thiruvananthapuram.

Design: Randomised placebo controlled double blind trial.

Participants: 108 term babies with post-asphyxial encephalopathy, stratified into three grades based on clinical criteria.

Intervention: The treatment group (n=54) received pyritinol and the control group (n=54) received placebo, in exactly the same increasing dosage schedule of 1 to 5mL liquid drug (20-100 mg) from 8th postnatal day until the end of six months.

Outcome variables: Mean Mental Development Index

(MDI) and mean Psychomotor Development Index (PDI) measured on Bayley Scales of Infant Development at one year of age.

Results: No statistically significant difference was observed in MDI or PDI scores at one year between the treatment and control groups. The confidence interval for the differences ranged from -6.3 to +8.7 for MDI and from -4.1 to +12.7 for PDI. On multiple regression analysis using one year MDI and PDI scores, even after controlling for birthweight, there was no statistically significant difference between the treatment and control groups.

Conclusion: Pyritinol is not useful in improving the neurodevelopmental status of babies with post-asphyxial encephalopathy at one year of age.

Keywords: *Neurodevelopmental outcome, Post-asphyxial encephalopathy, Pyritinol.*

Perinatal hypoxia has been recognized as a possible cause of mental and physical handicaps in childhood for more than 100 years(1). Approximately 23% of the 4 million annual global neonatal deaths are attributable to birth asphyxia(2). In a prospective cohort study undertaken in the principal maternity hospital of Kathmandu, an upper estimate for the prevalence of major neuro-impairment at 1 year, attributable to birth asphyxia was 1 per 1000 live births(3). The best predictive risk factors for the neurological prognosis at follow-up is reported to be severe perinatal asphyxia at birth and/or evidence of encephalopathy in neonatal period(4,5). Newborn

encephalopathy (Grades I, II and III), particularly with seizures and recurrent apnea, has been demonstrated to be an important predictor of subsequent motor and cognitive handicaps(6-9). Clinical presentation of birth asphyxia with severe newborn depression has demonstrated that most children who survived with sequelae had clinical signs of encephalopathy during the neonatal period(10).

Pyritinol or pyritinol dihydrochloride monohydrate, is a derivative of pyridoxine with a chemical structure of two pyridoxine molecules linked by a disulphide bridge and has only 0.1% of vitamin B6

activities. Benesova, *et al.*(11), based on a controlled trial of pyritinol, reported significant improvement in neurodevelopmental outcome at one year and every year after that till six years of age. However, this was not a controlled trial and hence the results, not conclusive. The drug was effective only if used early and for prolonged periods(12). This drug is not routinely used in our hospital nursery and during follow up, although pediatricians may use it in individual cases. Only a randomized controlled double blind trial can give a definite answer on the efficacy of pyritinol in perinatal asphyxia.

The broad objective of the study was to evaluate the efficacy of pyritinol in improving the neurodevelopmental outcome at one year of age among term babies with post-asphyxial encephalopathy, using Bayley Scales of Infant Development (BSID), the most widely accepted objective developmental assessment tool(13). The hypothesis tested in this randomized placebo controlled double blind trial was that the mean Mental Developmental Index (MDI) and the mean Psychomotor Developmental Index (PDI) scores obtained in BSID, for the group of term post-asphyxial encephalopathy babies receiving pyritinol is greater than for the control group of babies.

METHODS

A sample size of 54 in each group was calculated to detect a mean clinically significant difference of 16 in the MDI or PDI scores for two-tailed test with 90% power, significance level at 0.05 and with 5% drop-out rate(14). A pilot study was done on a sample of 15 babies with post-asphyxial encephalopathy.

The sequential criteria for inclusion in the study were: born in the labor room of Medical College, Thiruvananthapuram; completed 37 weeks of gestation; admitted to the special care nursery with a clinical diagnosis of birth asphyxia; clinical evidence of encephalopathy observed in the first 7 days of postnatal life; alive on 8th postnatal day; and, parents agreeing to randomization and monthly follow-up. The specific exclusion criteria were, total serum bilirubin more than 15mg/dL on the 7th postnatal day, blood glucose level less than 30mg/dL recorded on two occasions 4 hours apart any time

during the first 7 days of postnatal life, neonatal meningitis in the first 7 days of life, chromosomal anomaly, microcephaly, hydrocephalus, and any congenital anomaly known to affect growth and development.

The study was conducted with the approval of the ethical committee of the Medical College, Thiruvananthapuram. After obtaining the informed consent, participants were randomized on the 8th post natal day into treatment and control groups, using block randomization and separate random number series for the three grades to get the same number of treatment and control patients in each grade (I, II and III) of post-asphyxial encephalopathy. Serially numbered opaque envelopes, containing the allocation detail of a subject were developed at the Department of Biostatistics, Christian Medical College, Vellore.

Both the groups of babies received similar treatment as per the routine practice of the hospital till the 8th postnatal day. Eligible cases received, according to the randomized coding, placebo or active drug (pysitamol, 1 mL=20 mg) both having same consistency, colour and smell and the only difference being the batch number. The same dosage schedule was followed for drug and placebo and given orally as a single dose in the morning so as to avoid any possible sleep disturbances. A calibrated 1 ml medicine dropper was supplied for ease of administration of correct dose at home.

The increasing dosage schedule included 1 mL of the solution (placebo/pyritinol) per day from day 8 to day 30, increased by 1 mL every 15 days to 5 mL per day by day 76. This amount of the solution was continued till six months of age.

The parents were given a detailed discharge summary and a special Child Development Centre monthly follow-up schedule card. Contamination was avoided by checking the details of any medication received for more than one week. The medication bottle was brought along, collected and measured as an indicator of compliance. During the monthly follow-up visit, the mother was asked about any problem the baby had in the previous month and a thorough physical examination was done,

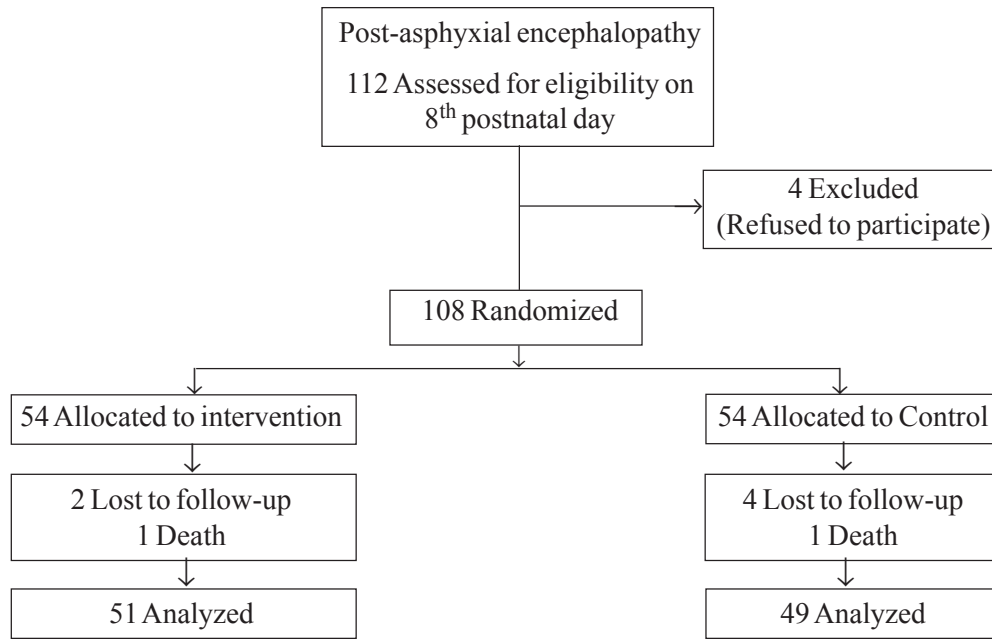


FIG. 1 Flow diagram of patients in the study.

specifically looking for any possible side effect of the drug. Any rash resembling a drug rash, clinical jaundice after one month of age, clinical increase in liver size at least 2cms more than on the previous visit and proteinuria (qualitatively reported as 2+ or above) were specifically noted.

The one year primary outcome measurement was Mental Development Index and Psychomotor Development Index obtained on the Bayley Scales of Infant Development (BSID), Baroda, India norms. BSID was administered in a separate quiet room by a well-trained observer blind to the treatment status of the babies. Every effort was made to adhere to the detailed instructions of the BSID test manual(13). The test items were presented in order of difficulty and those items passed were ticked, but added up only at a later stage to avoid any test bias. The raw scores obtained separately for mental scale and motor scale, by adding together the number of items passed on each scale separately, were then converted to MDI and PDI scores, respectively, using conversion tables provided in the test manual. Secondary outcome measurements at one year included weight taken without clothes, using a beam type of weighing machine calibrated against a standard weight once-a-week, length taken using a

simple infantometer, (with the baby supine, knees together and legs in a straight position) and, head circumference measured using a metal tape running through the most prominent part posteriorly and just above glabella anteriorly.

The criteria for loss to follow-up was not reporting for 1 year assessment of outcome variables even after sending two reminders to the home address and one to the alternative address at 7 days interval and evidence of having left the place. Quality check of the data being collected was done by perusal of individual data sheets at the weekly meetings of the research team. Out of 108 babies randomised on the 8th postnatal day, 100 babies (treatment group 51, control group 49) with outcome measurements available at one year, were included in the initial “intention to treat” analysis. All 100 babies had received the trial medication for periods of 75% or more of the total days the baby should have received the medication. Therefore, there was no need to consider any separate analysis of those with completed treatment. An analysis of the baseline characteristics was done using chi-square statistic and student’s *t*-test to look for any statistically significant differences between the treatment and control groups. To test the hypothesis

TABLE I COMPARISON OF TREATMENT AND CONTROL GROUPS AT RANDOMIZATION

Characteristics	Treatment (n=54) (SD)	Control (n=54) (SD)	P value
Encephalopathy			1.0
Grade I	47	47	
Grade II	5	5	
Grade III	2	2	
Abnormal delivery	27	27	1.0
Male: female ratio	32:22	34:20	0.34
Low birthweight (<2500g)	11	15	0.49
Low SE status	40	43	0.64
Mean weight at birth	2841 (513.1)	2627 (461.3)	0.02
Mean length at birth	48.1 (2.8)	48.0 (1.8)	0.76
Mean head circumference at birth	33.7 (1.9)	33.2 (1.1)	0.10
Mean gestational age	39.1 (1.3)	39.1 (1.3)	0.95
Days of nursery stay (mean)	3.7 (2.1)	4.0 (3.6)	0.70
Mother's education (years) (mean)	7.5 (3.2)	8.2 (2.9)	0.31
Father's education (years) (mean)	7.4 (2.6)	8.1 (2.6)	0.18

regarding MDI and PDI, Student's *t*-test was used to compare means of the two independent samples, after seeing that the data were approximately normally distributed. A 95% confidence interval for the true difference in population means was also calculated. Multiple regression analysis using MDI and PDI scores at one year of age was done with pyritinol/placebo and any baseline variable with significant difference between the groups, as explanatory variables.

The double blind nature of the study was strictly maintained at all stages of the trial. An independent person kept the coding about the treatment status of the patient. The parents of the babies, the neonatal consultant, the investigator, the research assistants and the outcome evaluators did not know the treatment status of the babies.

RESULTS

During the recruitment period of 17 months there were a total of 21,604 deliveries, with 349 babies with diagnosis of asphyxia. Of these, 155 did not develop post-asphyxial encephalopathy, 20 babies meeting exclusion criteria were excluded and 62 babies died in the labor room or nursery, leaving 112

cases of post-asphyxial encephalopathy available for randomisation on the 8th postnatal day. Excluding four babies whose parents expressed inability to come for monthly visits, 108 babies were randomised (**Fig. 1**). After block randomisation we could obtain only 5 each of grade II and 2 each of grade III encephalopathy, possibly because it is babies with severe asphyxia who are likely to develop grade II and III encephalopathy, who die early and cannot be saved without ventilator support.

Table I shows comparison of baseline characteristics of the two groups at the time of randomization. There was a statistically significant difference observed for the weight at birth between treatment and control groups. **Table II** shows no statistically significant difference in MDI or PDI scores at one year between the treatment and control groups. There were also no statistically significant differences observed between the treatment and the control groups on growth parameters of weight, height and head circumference. As a statistically significant difference was observed for the weight at birth between treatment and control groups, adjustment for this potential confounder was needed in the analysis of outcomes. On multiple regression

TABLE II COMPARISON OF MENTAL DEVELOPMENT INDEX SCORE, PSYCHOMOTOR DEVELOPMENT INDEX SCORE AND GROWTH PARAMETERS AT 1 YEAR

Score	Treatment Group (n=51) Mean (SE)	Control Group (n=49) Mean (SE)	Difference in Means (95% CI)	P value
Mental Development Index	91.6 (2.9)	92.8 (2.5)	1.2 (-6.3, +8.7)	0.75
Psychomotor Development Index	96.0 (3.2)	100.3 (2.7)	4.3 (-4.1, +12.7)	0.31
Weight (kg)	8.6 (0.2)	8.6 (0.2)	0.0 (-0.5, +0.5)	0.86
Length (cm)	71.9 (1.4)	72.1 (1.5)	0.2 (-3.8, +0.5)	0.94
Head circumference (cm)	44.8 (0.2)	45.0 (0.2)	0.2 (-0.4, +0.8)	0.63

analysis using one year MDI and PDI scores, even after controlling for birth weight there was no statistically significant difference between the treatment and control groups.

DISCUSSION

As physicians we always feel inadequate if we cannot offer drugs for a medical problem that we face and birth asphyxia is no exception. The drug pyritinol is widely used among asphyxiated babies by practitioners in India, South East Asia and some East European countries, even without strong evidence and hence this study is timely and appropriate. Availability of good objective outcome measurements is crucial for successful completion of any good trial. The objective neurodevelopmental measurement of MDI and PDI using Bayley scales of infant development standardized for the Indian population were used as the one-year outcomes in this study(14).

One of the main issues that we have to face when we try to relate asphyxia and outcome is the problem of defining post-asphyxial brain damage(15). We chose post- asphyxial encephalopathy as marker of asphyxia in this study because of the dual advantage of fairly accurate prediction of outcome and generalisability, as majority of neonatal units in India are level II without ventilation facilities.

This trial has failed to show any evidence to suggest that pyritinol is useful in improving the neurodevelopmental status at one year of age. For any negative trial result it is important to consider the following methodological issues. Firstly, did the

study have adequate power? The sample size calculated to detect a clinically significant difference of 16 MDI or PDI score with 90% power at 0.05 significance level was 96 and we have one year outcome measurements available for 100 babies. Secondly, did the study get adequate drug compliance? For all the babies for whom one-year outcome measurements were made, there was evidence that they had consumed more than 75% of the total expected drug/ placebo. Thirdly, did the study have mortality and or complications? There were two deaths one on the 58th day, a case of grade-III encephalopathy belonging to the control group, and the other baby belonging to the treatment group died at home due to bronchopneumonia, both likely to be unrelated to use of drug. None of the babies belonging to either the pyritinol or the control group had evidence of drug complications. This was the same as observed in the Prague study(11), suggesting that the drug is safe to be used in infants at doses below 100 mg per day.

Retrospective power calculations were done for MDI and PDI. The current power is 6% and 19% respectively. At the planning stage, the study group expected minimum of 16 units difference between the two arms as this was clinically meaningful difference and we wanted to achieve. However, the current power suggested that the Pyritinol arm is as good as control arm. This implied fact that the effect due to Pyritinol is absolutely nil. It is also evident that failing to reject the null hypothesis is not due to lesser numbers. Moreover, it is unwise to show a small difference in MDI to be statistically significant by recruiting thousands of children.

WHAT THE STUDY ADDS?

- Pyritinol does not improve neurodevelopmental status of babies with post-asphyxial encephalopathy at one year of age.

This study has failed to show any positive effect of pyritinol in improving the neurodevelopmental status of babies with post-asphyxial encephalopathy at one year of age. Therefore, widespread use of the drug should be discouraged not only for economic reasons but also for ethical reasons.

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