ORIGINAL ARTICLE

Developmental outcome of the use of etamsylate for prevention of periventricular haemorrhage in a randomised controlled trial

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Objective: To compare neurodevelopmental outcome of survivors of the multicentre trial of etamsylate (the iRNN for ethamsylate) for prevention of periventricular haemorrhage in very low birthweight infants.
Design: Double blind, single observer, prospective follow up of placebo controlled study.
Setting: Six neonatal intensive care units in the United Kingdom. Neurodevelopmental outcome was assessed in health premises or children's homes.
Subjects: 268 of 276 survivors of the original study were seen between 3.5 and 4.2 years of age. All were inborn and weighed 1500 g or less at birth.
Intervention: Etamsylate 12.5 mg/kg or placebo six hourly from within one hour of delivery for four days.
Main outcome measures: McCarthy scales of children's abilities, standardised neurological examination, full physical examination, functional assessment, seven letter Stycar vision test, and audiometry.
Results: There was no difference between the groups in neuromotor outcome (cerebral palsy) or in the general cognitive index (GCI) of the McCarthy scales (mean GCI was 93.3 for the etamsylate group (n = 133) and 89.7 for the placebo group (n = 131); p = 0.10). There were more children with GCI < 70 (9 *v* 19; p = 0.047) or $\leqslant 50$ (3 *v* 11; p = 0.03) in the placebo group. Fewer children in the etamsylate group had squints (17 *v* 30; p = 0.042) or required surgery for patent ductus arteriosus (1 *v* 8; p = 0.036).
Conclusions: Etamsylate was not associated with a reduction in cerebral palsy. Severe cognitive impairment was reduced, but more children died and the improvement may be because fewer survived with low GCI.

We have previously reported a large, randomised, double blind, placebo controlled, multicentre study evaluating the effect of etamsylate for the prevention of periventricular haemorrhage (PVH) in very low birthweight infants.[1] Our interest had arisen because of the known association between PVH in very preterm infants and the increased incidence of long term neurodevelopmental problems.[2 3] Etamsylate (the new iRNN for the drug originally called ethamsylate) has been used for many years in the prevention of capillary bleeding, and our previous study was designed to be of adequate size to show whether etamsylate could prevent PVH, as shown by cranial real time ultrasound scanning. The babies were recruited between December 1983 and February 1986. They were inborn infants weighing 1500 g or less at birth. Infants with lethal congenital malformations were excluded. The treated infants were given 12.5 mg/kg etamsylate per dose, the first dose given intravenously or intramuscularly within an hour of delivery, followed by six hourly doses intravenously for four days. The control infants were given placebo at identical times. The most severe grade of haemorrhage observed at any time was recorded, and scans were performed within two hours of birth and on days 3, 7, and 14 as a minimum. The ultrasound scans were graded as: 0, no haemorrhage; 1, subependymal haemorrhage; 2, intraventricular haemorrhage; 3, haemorrhage into brain parenchyma. We found a reduction in the occurrence of grades 2 and 3 haemorrhage from 29.8% in the control group to 18.5% in the treatment group, a reduction of nearly 40% ($p < 0.05$). No significant side effects were noted, and mortality was similar in the two groups.

Preventing intraventricular haemorrhage would only be of benefit if this was followed by a reduction in the incidence of neurological or neurodevelopmental problems in the survivors. It was therefore important to follow the progress of the children from the original study to see whether treatment with etamsylate was beneficial. The present study was organised to allow a single observer follow up of all the survivors from each of the five original centres (six units) at an age when most significant neurodevelopmental problems would be identified, but before risking the loss of too many infants from follow up.

METHODS

The children were traced with the help of health visitors, general practitioners, and family practitioner committees. The general practitioner was contacted for permission to see the families and to avoid contacting a family where the child had died. The parents were then approached by letter and asked to attend for a single assessment session at the appropriate hospital. If this proved impossible, the child was seen at home. A single observer (JS) performed all the assessments from each of the five centres. The study remained double blind. We aimed to see all the children between 3.5 and 4 years from the date of delivery. If the child was not available for assessment, the reason was recorded. The assessment consisted of a social and medical history, a developmental assessment using the McCarthy scales of children's abilities,[4] and a standardised neurological examination as described by Amiel-Tison and Grenier[5] and modified for 4 year olds.[6] A full physical examination, including height, weight, head circumference, and blood pressure, and a seven letter Stycar vision test were performed.

Abbreviations: GCI, general cognitive index; PVH, periventricular haemorrhage

The results of local audiometry were obtained, or this was requested if it had not already been performed. A specific note was made of the presence or absence of a squint and whether the child had had a shunt or other surgical treatment[7] for hydrocephalus. If a child was unable to perform the McCarthy scales because of severe neurological impairment, they were given the lowest score and included in the analysis. If a child did not cooperate but had no evidence of impairment, they were excluded from the analysis.

The neuromotor outcome was expressed using the regular classification for cerebral palsy (spastic quadriplegia, hemiplegia, diplegia, monoplegia and ataxic and hypotonic). A neurological score was also devised to allow a functional overall assessment of impairment or disability (table 1)—the severity of the abnormality found. McCarthy scales of children's abilities, neurological score, sensory assessments of vision and hearing, and presence or absence of treatment for hydrocephalus were used to classify the children as having a major or minor impairment or as normal (table 1). We classified a child as having a multiple major impairment if he/she had more than one reason to be classified as having a major impairment—that is, more than one of general cognitive index (GCI) < 70, neurological score grade 4 or 5, sensory-neural hearing loss requiring aids, or visual impairment 6/60 or worse despite correction. After examination of the distributions, the results were analysed using χ^2, Fisher's exact, and two sample tests on proportions for the attribute data and two sample t tests for the McCarthy scores,[8] as appropriate. Two tailed tests were used to compare the clinical features of the two groups and to analyse the responses. The study was approved by the ethics committee at each hospital.

RESULTS

A total of 360 children were enrolled in the original study. Figure 1 is a flow diagram of their involvement in the study. Eighty four died (23%), and 276 survivors were eligible for follow up. Table 2 gives the age at death, with the causes of death in those over 14 days (the causes of death up to 14 days have been published[1]). Of the 276 survivors, 268 (97%) were seen between 3.5 and 4.2 years of age. Table 3 gives the clinical data for the survivors. There is no significant difference between the groups for any of the data, although more parents in the placebo group were unemployed. The whereabouts and outcome of the eight children not seen are known (one twin pair refused, one in the placebo group and one in the etamsylate group, but both normal at 4 years of age when seen by a consultant paediatrician; two other refusals, one in the placebo group had a spastic quadriplegia and was under regular review by a consultant but one in the etamsylate group was at normal school; three (two in the etamsylate group) had emigrated but were normal at 1 year of age on hospital follow up; one traveller family (placebo group) was reported normal by the family).

Four children did not cooperate for the McCarthy scale; all four were believed to be normal and all four were in the placebo group. The results of the McCarthy scales of children's abilities in the remainder (table 4) showed a trend towards a higher GCI in the etamsylate group but this was not significant. This trend was due to the numbers of children with GCI < 70 in the placebo group (table 4), and this difference was significant (9 in the etamsylate group and 19 in the placebo group; $p = 0.047$). They are likely to require special education. The remaining children with GCI ≥ 70 had very similar GCIs (etamsylate group, 95.9; placebo group, 95.6). The numbers with GCI ≤ 50 was also greater in the placebo group ($3 \nu 11$; $p = 0.03$).

There was no difference between the groups in neuromotor outcome (cerebral palsy; table 5). The trend for GCI is the same if children with cerebral palsy are excluded, but it is not clinically or statistically significant. There were similar

Table 1 Neurological score (a functional assessment of impairment of disability) and our classification of impairment into three groups

Neurological score
- Grade 0, no impairment or disorder detected
- Grade 1, impairment or disorder detected but no apparent disability and requiring no treatment
- Grade 2, impairment or disorder detected with no apparent disability but requiring treatment
- Grade 3, impairment plus disorder but compensates well enough to cope
- Grade 4, impairment plus disorder requiring continuing treatment support or management
- Grade 5, impairment plus disorder preventing satisfactory functioning

Major impairment
- General cognitive index < 70
- Neurological score grade 4 or 5
- Sensory-neural hearing loss requiring aids
- Visual impairment of 6/60 or worse despite correction

Minor impairment
- General cognitive index 70–79
- Neurological score grade 1, 2, or 3
- Sensory-neural hearing loss not requiring aids
- The presence of amblyopia (visual acuity of 6/18 or worse)
- Treatment for hydrocephalus

Normal
- General cognitive index ≥ 80
- Neurological score of 0
- No sensory-neural hearing loss
- No amblyopia
- No hydrocephalus

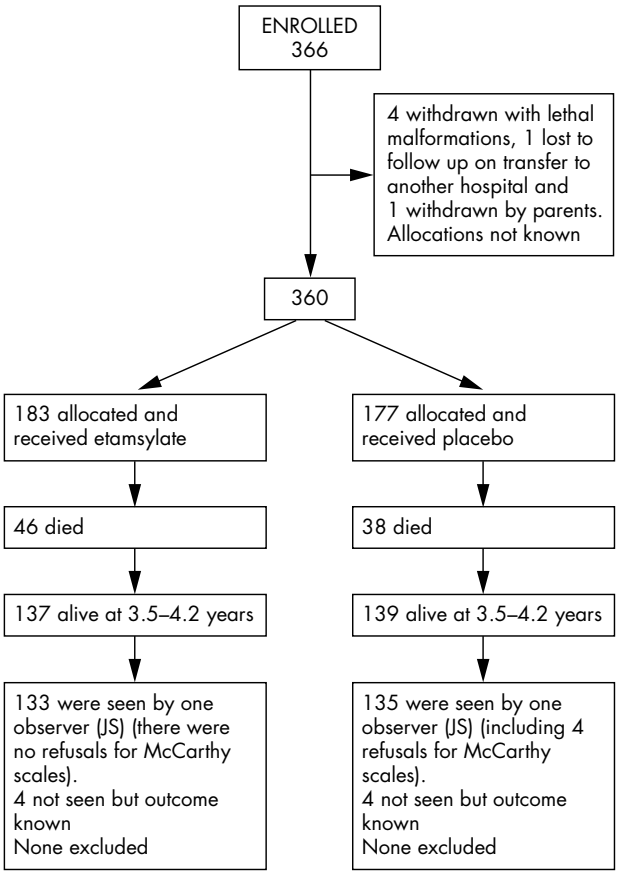

Figure 1 Flow diagram for children's progress through the trial.

Table 2 Age at death and sex for the whole study group and the cause of death for those dying after14 days. The cause of death for the remainder is given in the original paper[1]

	Etamsylate	Placebo
Age at death		
<7 days	26	23
7–28 days	11	5
>28 days	9	10
Total	46	38
Males	37	28
Females	9	10
Cause of death		
Lung disease	2	2
Septicaemia	4	4
Sudden infant death syndrome	2	1
Intestinal obstruction and ventriculitis	0	1
Renal failure	0	1
Shunt blockage	0	1
Perforation of bowel	0	1
Hypoplastic left heart	1	0
Unknown*	5	3
Total	14	14

*One child in the etamsylate group had a grade 2 haemorrhage, and one in the placebo group had a grade 3 haemorrhage.

numbers of children with major impairment in each group (18 in the etamsylate group and 22 in the placebo group), but the number of children with multiple major impairment was less, but not significantly so, in the etamsylate group (4 *v* 11; Fisher exact test p = 0.067). However, if survival with a lack of major impairment is considered the best outcome, there is no difference between the groups (119 or 65% in the etamsylate group and 116 or 66% in the placebo group, including the unseen quadriplegic child). Three children in the etamsylate group and one in the placebo group were registered blind. There were four children in the etamsylate group and two in the placebo group with sensory-neural hearing loss requiring aids. There were 17 children in the etamsylate group who had a squint compared with 30 in the placebo group (p = 0.042; χ^2 test). There was one child in the etamsylate group who required surgery for patent ductus arteriosus compared with eight in the placebo group (p = 0.036, Fisher's exact test). Two children in the etamsylate group and nine in the placebo group required treatment for hydrocephalus (not significant).

DISCUSSION

Etamsylate (diethylammonium-2,5-dihydroxysulphate) is an extremely safe drug. We discussed the pharmacology in our previous paper.[1] We report a large single observer follow up study of intervention for PVH. The initial trial showed a reduction in PVH in the etamsylate group,[1] and, in 1993, 25% of neonatal units in the United Kingdom were using etamsylate in very low birthweight infants. However, etamsylate would be of limited clinical use if this was not accompanied by an improved long term outcome. When the trial started, the severity of neurodevelopment problems was thought to be related to PVH.[2 9 10] At this stage the relevance of periventricular leucomalacia was unknown. Later work has shown that uncomplicated PVH is often associated with normal neuromotor outcome,[11 12] but the ultrasound appearance associated with periventricular leucomalacia is more predictive of motor impairment.[13]

The single observer method has eliminated the interobserver error often found in multicentre trials.[14] We report a large study with a very high follow up rate and a control group comparable to the treatment group. High ascertainment rates are important because there is some evidence that children

Table 3 Baseline data for the 268 survivors seen

Baseline data	Etamsylate	Placebo
Singleton/multiple birth	97 (73%)/36 (27%)	97 (72%)/38 (28%)
Male/female	50 (38%)/83 (62%)	65 (48%)/70 (52%)
Birth weight (g)*	1154 (210)	1166 (217)
Gestational age (weeks)*	29.5 (2.3)	29.6 (2.4)
Apgar score (5 min) <7	18 (13.5%)	24 (17.8%)
Caesarean section	73 (55%)	83 (61%0
Respiratory distress†	80 (60%)	88 (65%)
Artificial ventilation†	89 (67%)	96 (71%)
Acidosis pH <7.15†	40 (30%)	34 (25%)
Hypercapnoea ($PaCO_2$>60 mm Hg or >8.2 kPa)	40 (30%)	36 (27%)
Pneumothorax†	4 (3%)	5 (4%)
Grade 3 PVH	11 (8%)	13 (10%)
Grade 2 PVH	16 (12%)	20 (15%)
Grade 1 PVH	15 (11%)	10 (7%)
No PVH	91 (68%)	92 (68%)
Maternal smoking	59 (44%)	55 (41%)
Maternal age at birth (years)*	27.8 (5.8)	26.9 (6.0)
Centre		
Bath	11 (8%)	12 (9%)
Blackburn	21 (16%)	25 (18%)
Bristol (BMH & Southmead)	40 (30%)	40 (30%)
Cardiff	15 (11%)	11 (8%)
Liverpool	46 (35%)	47 (35%)
Social class		
1	3 (2%)	7 (5%)
2	22 (17%)	15 (11%)
3	65 (49%)	61 (45%)
4	14 (10%)	6 (4%)
5	3 (2%)	1 (1%)
Unemployed	26 (20%)	45 (34%)
Total	133	135

*Standard deviation in parentheses.
†In first four days.
PVH, Periventricular haemorrhage.

Table 4 Data on McCarthy scales of children's abilities

	Etamsylate (n = 133)	Placebo (n = 131)	p Value
GCI	93.3 (16.2)	89.7 (19.7)	0.10
Subscales			
Verbal	45.9 (9.6)	43.6 (11.1)	0.07
Perceptual/performance	48.4 (9.7)	46.6 (11.3)	0.17
Quantitative	45.2 (9.6)	44.6 (11.1)	0.6
Motor	43.3 (9.8)	41.0 (10.8)	0.07
Memory	44.7 (8.5)	42.7 (10.0)	0.07
Mean GCI excluding those with a score ⩽50	94.3 (14.9)	93.3 (16.2)	0.6
GCI⩽50*	3	11	0.03
Mean GCI in those with a score ⩾70	n = 124 95.9 (13.3)	n = 112 95.6 (14.2)	0.86
GCI<70*	6 Boys, 3 girls	8 Boys, 11 girls	
Total	9	19	0.047
Mean GCI in those without cerebral palsy	n = 116 95.2 (15.3)	n = 116 93.1 (17.1)	0.33
Mean GCI in those without grade 2 or 3 IVH	n = 106 94.8 (15.4)	n = 99 92.2 (17.9)	0.27

Values are mean (SD). The standardised mean for the subscales is 50 in normal children and 100 for the GCI. There is a non-significant trend for the GCI and the subscales to be higher in the etamsylate group, using two sample *t* tests. This difference is due to the greater number of children in the placebo group with GCI ⩽ 50 (and < 70). Fisher's exact test was used to compare the numbers in each group.
*Four in the placebo group and one in the etamsylate group were too severely affected to have a score. There were four who refused to cooperate for the McCarthy scales and all were excluded: all four were in the placebo group.
GCI, General cognitive index; IVH, intraventricular index.

Table 5 Neuromotor outcome (cerebral palsy) and major impairment in survivors seen

Outcome	Etamsylate (n = 133)	Placebo (n = 135)
Spastic quadriplegia	4	7
Spastic hemiplegia	7	4
Spastic diplegia	3	2
Spastic monoplegia	1	0
Ataxic	1	0
Hypotonic	0	1
Total with cerebral palsy	16	14
Major impairment		
Boys	12	11
Girls	6	11
Total	18	22
Multiple major impairment		
Boys	3	4
Girls	1	7
Total	4	11
Multiple major impairment and grade 2 or 3 IVH	3	9

There is no reduction in cerebral palsy in the etamsylate group. Multiple major impairment is a subset of the major impairment group. One child in the placebo group not seen but known to have a quadriplegia is not included.
IVH, Intraventricular haemorrhage.

who are difficult to trace may be at higher risk of an abnormal outcome.[15] In this study, the outcome of all the unseen survivors is known, and no survivors were excluded from follow up. If the unseen survivors are entered into the analysis, the results are unchanged.

It is unfortunate that the randomisation resulted in fewer boys in the etamsylate group as boys are known to have a poorer developmental outcome. However, we do not believe this has affected the results because the girls in the placebo group did badly both for major impairment and in having a GCI < 70. Neither was there an excess of deaths among boys in the etamsylate group.

The trend to a lower GCI in the placebo group was due to the difference in the number of children with a GCI < 70 and particularly to those with a GCI $\leqslant 50$. A difference in the neuromotor outcome (cerebral palsy) might have been expected and was our hypothesis, because of the initial difference in PVH between the groups, but this was not found. The likelihood of survival without a major impairment was similar in both groups because of a small imbalance between the groups for death and for major impairment, with more deaths in the treatment group and more impairment in the placebo group. We believe these differences have arisen by chance, but it is possible that etamsylate may have decreased the chance of survival with a major impairment. This is not supported by the follow up of the EC trial, in which deaths were similar in the etamsylate and placebo groups.[16] The EC trial also failed to detect any long term benefit of etamsylate treatment, but did not report on the incidence of patent ductus. They did not find a reduction in the number of squints.

It may be that PVH represents a marker for perinatal cerebral insults of varying types. PVH is associated with a diminution in the blood flow to the developing brain.[17 18] During ischaemia and perinatal asphyxia, cerebral blood flow is reduced. As cerebral blood flow falls, metabolic disturbances result, ultimately leading to the prostaglandin synthetic cascade of ischaemia medicated prostaglandin production.[19] By inhibiting the effects of prostaglandins, etamsylate may exert an effect by closing the patent ductus and thereby increasing cerebral blood flow.[20] We have found a significant difference in the number of children with patent ductus arteriosus. Etamsylate may also have an effect on the microcirculation, encouraging platelet aggregation and vasoconstriction and therefore haemostasis. It also inhibits the effects of the prostaglandin mediated vasodilatation and increased capillary permeability, thereby reducing oedema secondary to capillary leakage. It is also possible that etamsylate would reduce reperfusion haemorrhage in ischaemic areas of the brain, preventing secondary damage.

Although we are uncertain of the exact mechanism of action of etamsylate, we know that it may reduce the incidence of PVH in very low birthweight infants.[1 21 22] We have found that it also reduces the incidence of patent ductus arteriosus and squint. It may have a role in improving the neurodevelopmental outcome of very low birthweight infants, reducing the numbers of those with severe cognitive impairment (GCI < 70). Although this hypothesis is not supported by the EC study,[16] the follow up in that study was at 2 years of age performed by local paediatricians and with large numbers of children lost to follow up. Etamsylate probably closes the ductus arteriosus but does not reduce the incidence of cerebral palsy—our original hypothesis.

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