Randomised controlled trial of prophylactic etamsylate: follow up at 2 years of age

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Abstract

***Aim*—To assess the role of etamsylate* in reducing the risk of haemorrhagic brain damage and its consequences.**

***Design*—Follow up of babies recruited into a randomised controlled trial.**

***Methods*—A total of 334 infants born before 33 weeks gestation in France and Greece were randomly allocated within the first four hours of birth either to receive etamsylate or to act as controls. The principal outcomes in the trial were death or impairment and/or disability at the age of 2 years.**

***Results*—Fifty nine children were lost to follow up. A total of 115 (34%) either died or had some impairment or disability, and 88 (26%) either died or had severe impairment or disability at 2 years of age. These outcomes did not differ significantly between the two randomised groups: relative risks and 95% confidence intervals 1.14 (0.78 to 1.4) and 1.17 (0.82 to 1.68) respectively. The findings were similar for all the prespecified subgroup analyses stratified by key prognostic factors at trial entry: country of birth, gestational age < or ⩾ 29 weeks, inborn or outborn, age < or ⩾ 1 hour, and with or without cerebral scan abnormality.**

***Conclusion*—These findings do not support the use of etamsylate. Other strategies need to be evaluated for the prevention of mortality and morbidity in these vulnerable infants.**

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Keywords: etamsylate; ethamsylate; preterm; brain; periventricular/intraventricular haemorrhage; childhood disability; randomised controlled trial

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Haemorrhagic brain damage (periventricular or intraventricular haemorrhage (PIVH)) is common in infants born early. This damage can lead to death or later impairments and disabilities, with all the consequent burdens on the health services and families.[1] Preventive measures may be considered in both the antenatal and neonatal periods. Antenatal prevention, however, may reach babies born at term as well as the target preterm population, and so is potentially wasteful of resources. Neonatal interventions to infants actually born preterm therefore have potential advantages.

In the 1980s, the results of two randomised controlled trials[2 3] suggested that prophylactic etamsylate may be effective in reducing haemorrhagic damage. Consequently, in 1990–1991, we conducted an EC funded trial in France and Greece. In 10 neonatal units, 334 babies born before 33 weeks gestation were randomly allocated within 4 hours of birth to receive either 16 doses of etamsylate over four days or no etamsylate. This was before the surfactant era, and around 25% of this trial population died or had evidence of major cerebral problems. This outcome did not differ significantly between the two randomised groups (relative risk (RR) 1.17; 95% confidence interval (CI) 0.82 to 1.65).[4] Two further trials have been reported. In a trial including 171 babies, Chen[5] found a benefit of etamsylate in reducing PIVH and severe PIVH. In contrast, an abstract from a trial of 150 babies did not find any such benefit.[6]

The prespecified principal outcome for the EC trial was not these short term effects, however, but their implications in the longer term. This paper therefore reports the results of a follow up for the surviving children at the age of 2 years.

Methods

As part of the planned routine follow up in paediatric outpatient clinics of children who had been in neonatal intensive care, it was planned to assess the health and development of surviving children at the age of two years. In France, the paediatrician was "blind" to the treatment allocation and so usually was the paediatrician in Greece.

When a child from the trial was approaching 2 years of age, the parents were asked to bring him/her to the follow up clinic. They were asked to complete a questionnaire on their child's development and health service usage.

The paediatrician at the clinic recorded information about neuromotor impairment and disabilities, developmental level, seizures, and growth, and then returned the information and the parental questionnaire to Oxford for data processing and analysis. Reminders were sent for any overdue datasheets, and the national coordinators contacted local clinicians.

The principal outcome was death or disability at 2 years. A child was considered to have neuromotor impairment if so classified by the paediatrician and/or there was evidence of increased, decreased, or variable tone. A child who, in addition, was unstable sitting, needed help to walk, or had difficulty using one or both hands was classified as having neuromotor impairment with moderate disability. A child who could not sit unsupported, could not stand

*This is the rINN (Recommended International Non-propriety Name) for ethamsylate.

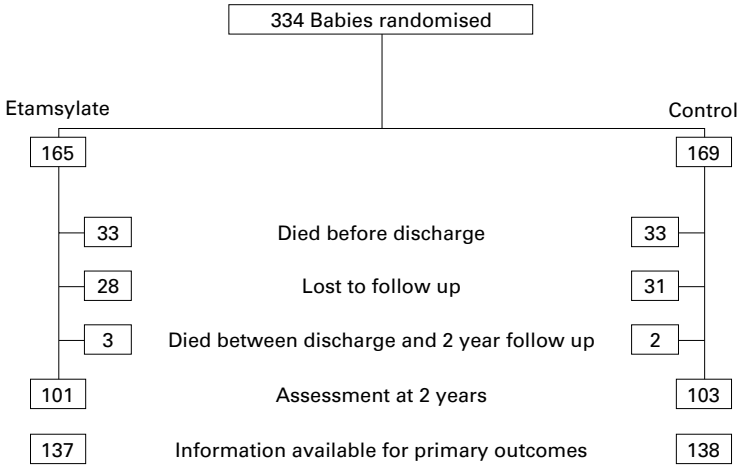

Figure 1 Derivation of children in the 2 year follow up.

or walk, or had very little hand use was classified as having neuromotor impairment with severe disability (functional loss). Developmental delay was classified as mild if less than six months behind, moderate if 6–12 months behind, and severe if more than 12 months behind. Overall, severe disability was defined as neuromotor impairment plus severe functional loss, or severe vision loss, or sensorineural hearing loss with aids, or severe developmental delay.

Primary analyses are based on all babies in the trial, within their randomly allocated groups (intention to treat analysis). Prespecified secondary analyses for the main outcomes are stratified by country, gestational age at trial entry (< 29 or ⩾ 29 completed weeks), inborn or outborn, age at trial entry (⩽ 1 or > 1 hour), and cerebral scan abnormalities known at trial entry. Where appropriate, comparisons are expressed as RRs with 95% CIs and medians and inter-quartile ranges (IQRs), with the median test.

Results

Of the 334 babies randomised, 66 (19.8%) died before discharge from hospital. Fifty nine children (17.7% overall or 22.0% of those discharged alive) were considered to be lost to follow up. The loss was very similar in the two trial arms (fig 1).

Five children (1.5%) were known to have died between discharge and the 2 year follow up. The causes of the three deaths in the etamsylate group were given as extensive severe bronchopulmonary dysplasia, sudden death (microcephaly), and possible sudden infant death syndrome. The two deaths in the control group were recorded as sudden death (regurgitation and pulmonary dysplasia, with spastic tetraplegy) and impaction of bowel with strangulated hernia.

Information was available for 204 surviving children at the 2 year follow up. The median age at assessment for both groups was 106 weeks (IQR 103–113). For five children (two receiving etamsylate, three controls), no follow up information was available from the local paediatrician, but was ascertained from the parental questionnaire.

Table 1 gives information about the characteristics of the babies at trial entry and their use of etamsylate, for all those randomised and for those assessed. Those who died were more likely than the survivors to have been of lower birth weight and shorter gestational age, to have had cerebral problems on ultrasound, and to have not completed the full 16 dose course of etamsylate. The children lost to follow up did not differ significantly between the two trial arms, and seemed more similar to those assessed at 2 years of age than to those who died (data available but not shown).

ASSESSMENT AT 2 YEARS OF AGE

Some 14% of those assessed had some neuromotor impairment, 9.3% had neuromotor impairment with moderate or severe motor

Table 1 Comparison of all randomised, and survivors assessed at 2 years of age: characteristics at trial entry and etamsylate use

	All randomised		*Assessed*	
	Etamsylate (n=165)	*Control (n=169)*	*Etamsylate (n=101)*	*Control (n=103)*
Country:				
France	90	91	52	54
Greece	75	78	49	49
Age at randomisation (min):				
<60	18	21	10	13
60–119	55	46	32	24
⩾120	91	101	59	65
Gestational age: <29 weeks	31	35	17	14
Birth weight: <1500 g	114	118	62	70
Sex: male	84	91	50	56
Plurality: multiples	37	38	26	25
No with PIVH	57	62	32	30
No with cerebral problem on scan	57	61	33	31
No with major cerebral problem on scan	21	21	13	8
Fetal presentation: cephalic	98	115	60	72
Mode of delivery: vaginal	88	80	52	49
Steroids	31	22	21	14
Etamsylate doses:				
0	4	168	1	102
1–15	25	0	3	0
16	136	1	97	1

PIVH, Periventricular/intraventricular haemorrhage.

Table 2 Survivors assessed at 2 years: neuromotor impairment and developmental status, vision, hearing and medical problems, and growth

	Etamsylate (n=101)	*Control (n=103)*
Neuromotor impairment		
Tone changes in		
4 limbs	8	2
3 limbs	3	0
2 limbs		
Ipsilateral	1	2
Contralateral	3	4
1 limb	1	1
Tone change present but unclassifiable	1	3
No neuromotor impairment	81	89
Not known	3	4
Neuromotor impairment ± disability		
Impairment but no disability	5	5
Moderate disability	7	5
Severe disability	5	2
Developmental status		
No delay	87	85
Mild delay	4	7
Moderate delay	3	4
Severe delay	5	3
Not known	2	4
Vision\ocular problems		
Squint	19	15
ROP	3	1
Refractive error	5	2
Other	1	0
Normal vision	90	88
Not fully corrected by glasses	0	1
Low vision	1	1
See light only or blind	1	0
Not known	9	13
Hearing		
Sensorineural hearing loss:	1	0
Conductive hearing loss	1	0
Hearing aids	0	0
Seizures or on anticonvulsants	3	3
Drug treatment		
Bronchodilators	7	12
Other medication	5	6
Weight		
<3rd centile	20	17
3–10th centile	16	18
10–90th centile	56	50
>90th centile	2	2
Not known	7	16
Length		
<3rd centile	18	22
3–10th centile	18	14
10–90th centile	58	56
>90th centile	3	3
Not known	4	8

Growth estimates based on Growth Foundation Standards (Cole TJ, Freeman JV, Preece MA. British 1990 growth reference centiles for weight, height, body mass index and head circumference fitted by maximum penalized likelihood. *Stat Med* 1998;**17**:407–29).
ROP, Retinopathy of immaturity.

disability, and 7.3% were classified as having moderate or severe developmental delay (table 2). Differences between the randomised groups were not significant as shown by RRs and 95% CIs of 1.44 (0.73 to 2.67), 2.04 (0.80 to 5.23), and 1.17 (0.44 to 3.09) respectively.

Thirty four children had squints, but only two children in each trial arm had poor vision, and none wore hearing aids. Six had seizures or were taking anticonvulsant medication, and 30 had some medication (mainly bronchodilators). There was no evidence of statistically significant differences between the two trial groups. Over a third of the children in both groups were below the 10th centile for height and weight (table 2).

Table 3 shows the overall status of these children in mutually exclusive categories. Most (145) were assessed as "normal", and a further eight had neuromotor impairment without functional loss. Twenty one had neuromotor impairment with disability or with impairment(s) in other domains.

Table 3 Survivors assessed at 2 years: overall status (mutually exclusive categories)

	Etamsylate (n=101)	*Control (n=103)*
Normal	73	72
Neuromotor impairment with no disability	5	3
Neuromotor impairment		
With moderate disability	2	3
With severe disability but no impairment in other systems	1	1
With severe disability (other systems not known)	1	0
No neuromotor impairment but disability in other fields		
Deafness		
Vision loss	1	0
Moderate	0	1
Severe	1	0
Global developmental delay		
Mild	1	6
Moderate	2	3
Severe	0	0
Multiple system involvement		
Neuromotor impairment (± disability) with impairment in other fields	8	5
No overall status available	6	9
Any impairment or disability	22	22
Severe disability	11	6

Table 4 Survivors assessed at 2 years: health service use between discharge and 2 years

	Etamsylate (n=101)	*Control (n=103)*
Visits to specialists		
Paediatrician	49	54
Eye specialist	54	56
Ear specialist	26	22
Neurologist	33	36
Surgeon	8	17
Physiotherapist	31	22
Speech therapist	2	0
Hospital re-admissions		
1	19	21
⩾2	19	18

Over a third of these children were readmitted to hospital, and about half had outpatient visits to paediatricians and/or eye specialists (table 4).

PRINCIPAL OUTCOMES

In terms of the principal outcome, 35.2% of children in the etamsylate group either died or had some impairment or disability, compared with 33.7% in the control group (table 5; RR 1.14; 95% CI 0.78 to 1.4). If this composite outcome is restricted to those with severe problems—that is, death or severe disability—there is still little evidence of a substantial benefit of a policy of neonatal etamsylate (45/165 *v* 39/169; RR 1.17; 95% CI 0.82 to 1.68). This conclusion is similar in each of the stratified analyses in table 5 (interaction tests $p > 0.05$).

Only if we were to make extreme assumptions such as that 60% or more of those in the control group and none in the etamsylate group (or 100% in the controls and 40% in the etamsylate group) had adverse outcomes would we be able to show any statistically significant benefit of etamsylate.

Table 5 Principal outcomes: for total trial population, and stratified by country, completed weeks gestation at delivery, inborn/outborn, age at entry, and with or without cerebral scan abnormality at trial entry

	Etamsylate (n=165)	*Control (n=169)*
Known death or impairment or disability	58/165 (35)	57/169 (34)
France	33/90 (37)	30/91 (33)
Greece	25/75 (33)	27/78 (35)
<29 completed weeks gestation at delivery	18/31 (58)	18/35 (51)
=29 completed weeks gestation at delivery	40/134 (29)	39/134 (29)
Inborn	18/62 (29)	25/73 (34)
Outborn	40/103 (39)	32/96 (33)
Age at entry		
<1 hour	6/21 (29)	10/23 (43)
⩾1 hour	51/143 (36)	47/145 (32)
Not known	1/1 (100)	0/1 (0)
With cerebral scan abnormality at trial entry	23/57 (40)	30/61 (49)
Without cerebral scan abnormality at trial entry	35/108 (32)	27/108 (25)
Known death or severe impairment or disability	47/165 (28)	41/169 (24)
France	25/90 (28)	19/91 (21)
Greece	22/75 (29)	22/78 (28)
<29 completed weeks gestation at delivery	15/31 (48)	17/35 (49)
=29 completed weeks gestation at delivery	32/134 (24)	24/134 (18)
Inborn	15/62 (24)	20/73 (27)
Outborn	32/103 (31)	21/96 (22)
Age at entry		
<1 hour	5/21 (24)	7/23 (30)
⩾1 hour	41/143 (29)	34/145 (23)
Not known	1/1 (100)	0/1 (0)
With cerebral scan abnormality at trial entry	20/57 (35)	22/61 (36)
Without cerebral scan abnormality at trial entry	27/108 (25)	19/108 (18)

Values in parentheses are percentages.

Discussion

Etamsylate prevents capillary bleeding during surgery for adults, and therefore may reduce PIVH in preterm neonates. Horbar[7] has summarised possible mechanisms of action in terms of stabilisation of capillary membranes and an increase in platelet adhesiveness. It may also have direct effects on the cerebral vasculature by inhibiting prostaglandin synthesis, and indirect effects by closing the patent ductus arteriosus, as suggested in a small trial by Amato *et al*.[8]

The importance of PIVH is as a predictor of longer term outcomes. In this study, 31% of the 268 babies who had survived to the time of discharge from hospital had been diagnosed with PIVH (with the remainder either known not to have such haemorrhaging or whose haemorrhage status was not known). The status at 2 years of age of 74 of the 268 was not known. On the basis of the remaining 194 children, a diagnosis of PIVH did not appear to significantly raise the risk of the primary adverse outcomes used in the trial. The risk of death or severe impairment or disability was 13.3% (8/60) in the PIVH group compared with 10.4% (14/134) in those without such a diagnosis (RR 1.2; 95% CI 0.66 to 2.19). Similarly, the risks of death or any impairment or disability were 30% (18/60) compared with 23.1% (31/134) (RR 1.27; 95% CI 0.81 to 1.98). Given the imperfect predictive value of PIVH as the main outcome for this trial, the follow up reported here clearly adds useful information about longer term implications of interventions in the neonatal period. This paper is currently the only published follow up from a trial of neonatal etamsylate. Provisional findings from the four year follow up from the UK multicentre trial were reported in abstract[9] but not published in full.

Key messages

- The findings from the only published follow up of children from a randomised controlled trial of etamsylate do not support its use when given within the first four hours of birth to infants born before 33 weeks gestation
- Centres in Greece and France recruited 334 infants into the trial, and did not find that etamsylate reduced the risk of haemorrhagic brain damage or its consequences in terms of death or impairment and/or disability
- Other strategies need to be evaluated for the prevention of mortality and morbidity in these vulnerable infants

A third of the children in the EC trial died or were classified as having an impairment or disability at the age of 2 years. There is little evidence from this trial, however, that a policy of neonatal etamsylate would reduce the burden on their parents or on the health services.

There are a number of possible reasons for this finding. It could be that more children in the control group who were lost to follow up suffered an adverse outcome. This seems unlikely given the similarity in loss to follow up between the randomised groups.

It could be that a potential lack of blinding to allocation in Greece led to a bias in the paediatrician's assessment of the child's status. Again, this seems unlikely, partly because such bias was more likely to be in favour of etamsylate (the experimental treatment), and partly because the findings in France and Greece are similar.

Another possibility could be that the beneficial effects of etamsylate were diluted because it was not given soon enough after birth. This hypothesis is not supported by the analysis stratified by age at randomisation.

Perhaps the trial population, by including babies who, at 31 and 32 weeks gestation, had a relatively high chance of a good outcome, was not at sufficiently high risk. This seems unlikely to be a reason because about a third of the babies had a bad outcome, and the analysis stratified by gestational age did not suggest a greater effect in the lower gestational age group.

Alternatively, perhaps the population was at too high a risk, given that nearly a third already had cerebral problems on scans at the time of trial entry. Analysis of the primary outcomes stratified by known cerebral problems were, however, unable to detect a significant benefit of etamsylate.

It may be that, had the assessment been performed by a research developmental paediatrician in the child's home rather than in a normal follow up clinic, more subtle effects may have been detected. However, this would apply equally to babies in both trial arms.

Although this is the largest trial of neonatal etamsylate, it may still not be powerful enough

to detect uncommon effects. The 95% confidence intervals are still wide and so can only exclude the possibility of a benefit if it was less than about 20–25%.

The most likely reason for not being able to detect a sizeable benefit of the etamsylate policy in this trial is that such a benefit does not exist. Alternative strategies such as neonatal indomethacin[10] and delayed umbilical cord clamping[11] still need to be evaluated in well designed studies.

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