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Randomised trial of early tapping in neonatal posthaemorrhagic ventricular dilatation

Ventriculomegaly Trial Group

National Perinatal
Epidemiology Unit,
Radcliffe Infirmary,
Oxford
Ventriculomegaly
Trial Group
Coordinating Centre

Correspondence to:
Dr A Whitelaw,
Ventriculomegaly
Trial Group
Coordinating Centre,
National Perinatal
Epidemiology Unit,
Radcliffe Infirmary,
Oxford OX2 6HE.

Abstract
Treatment of posthaemorrhagic ventricular dilatation by early repeated cerebrospinal fluid taps was compared with conservative management in a randomised controlled trial of 157 infants in 15 centres. Thirty infants died and six moved abroad before follow up. During the first 14 days after randomisation, the early treatment group had five times more taps, and 12 times more cerebrospinal fluid removed. Infection of the cerebrospinal fluid occurred in seven of the early treated and four of the conservatively managed infants. Of survivors, 62% in both groups ultimately had ventricular shunts.

Neurodevelopmental assessment of survivors at 12 months was carried out by a single experienced examiner. Of survivors, 103 (85%) had abnormal neuromotor signs and 88 (73%) had disabilities. There was no detectable benefit of early treatment for children who did not have parenchymal lesions at the time they entered the trial. Nearly all those with parenchymal lesions had neuromotor impairment, but early treatment was associated with a significant reduction in other impairments.

Progressive ventricular dilatation leading to hydrocephalus is a serious complication of cerebral intraventricular haemorrhage in preterm infants. More than half the survivors into childhood have cerebral palsy, and a third have global developmental delay.[1–4]

Posthaemorrhagic ventricular dilatation is thought to result from obstruction of the cerebrospinal fluid pathways, and arachnoid villi, by multiple small clots. Later, basal cistern arachnoiditis may produce permanent obstruction leading to hydrocephalus.[5] Ventricular size can be monitored easily by repeated real time ultrasound measurements of ventricular width, and centile values are available relating this to gestational age.[6]

Progressive ventricular dilatation and head enlargement is usually accompanied by some increase in cerebrospinal fluid pressure, although the upper limit of normal (0·80 kPa or 6 mm Hg) is only slightly exceeded in some affected infants.[7] It is not known to what extent additional neurological damage may result from a period of raised ventricular pressure. Increased cerebrospinal fluid pressure may cause periventricular oedema, distortion of developing pathways, and decreased cerebral perfusion; many of the affected infants may, however, have already sustained cerebral hypoxic-ischaemic damage in the perinatal period, which is likely to result in later impairments.

If cerebrospinal fluid pressure is raised, removal of some of the fluid over a number of days might improve the long term outcome. Impairment might be prevented, or, if hypoxic-ischaemic damage has already occurred, its extent might be limited to that caused by the pre-existing lesion. Observational studies[3] [4] [8–10] have suggested that serial removal of cerebrospinal fluid may improve long term outcome, but no benefit of such treatment in reducing the need for surgical shunting was detected in two small randomised controlled trials.[11] [12] Dykes et al carried out a randomised trial of early treatment by lumbar puncture compared with close observation.[13] Severe posthaemorrhagic hydrocephalus was assessed by visual assessment of computed tomography or ultrasound scanning rather than by a quantitative method. Thirty eight asymptomatic infants were randomised of whom 31 survived. Among the 29 infants examined at 3–6 years of age there was a lower proportion of children with major handicap in the group that had received early treatment, but the small numbers involved did not reach statistical significance.

Repeated removal of cerebrospinal fluid may carry risks, such as infection and apnoea. Drainage by lumbar puncture, even if initially successful, may not be possible in some babies,[11] [12] and ventricular taps may then be necessary to reduce pressure, thereby increasing the risks further. Small ill infants are not usually suitable for immediate permanent shunts and there is a high risk of shunt infection. A high concentration of protein in the cerebrospinal fluid is an additional reason for delaying shunt surgery, because it predisposes to blockage of the shunt.[14]

Because of the uncertainties about the value of early treatment, we mounted a large, multicentre randomised trial in which early mangement of posthaemorrhagic ventricular dilatation by repeated cerebrospinal fluid taps was compared with conservative management. The principal outcome measure was the long term neurodevelopmental condition in the survivors. We report here the results of the trial up to the (corrected) age of 12 months.

Patients and methods
Infants with posthaemorrhagic ventricular dilatation were recruited from 15 centres during the three years, 1984–7. The final protocol was agreed by one neonatologist responsible for the trial in each of the participating centres and

then approved by each local research ethics committee. In some centres, signed parental consent was required; in others a verbal explanation was considered more appropriate.

ELIGIBILITY
Infants were eligible if all the following criteria were met: (*i*) there was haemorrhage into the ventricles identified by ultrasound scan; (*ii*) the ventricular width (midline to lateral border of the ventricle) was below the 97th centile[6] on the first scan, or the first scan showed clot distending the ventricle above the 97th centile (the measurement was taken from the midline to the lateral border of the lateral ventricle at the level of the interventricular foramina on a coronal scan); (*iii*) serial measurements of ventricular width had shown a progressive increase; and (*iv*) the most recent measurement of ventricular width had reached 4 mm over the 97th centile. In the case of asymmetrical dilatation, the measurement of the smaller ventricle was taken.

These criteria were based on the experience of members of the group who suggested that about half the infants meeting these criteria would eventually require surgical shunts.

TREATMENT ALLOCATION
After criteria of eligibility had been confirmed, babies were entered into the trial by telephoning the Clinical Trial Service Unit in Oxford. The clinician first gave details of identification and was then told the treatment allocation. Random allocation to either early treatment with taps, or conservative management, was organised in balanced blocks of six, stratified by centre.

TREATMENT SCHEDULES
Early treatment
The object of early treatment was to prevent further ventricular dilatation. A lumbar puncture was carried out and cerebrospinal fluid allowed to drain until a maximum of 2% of the body weight had been drained. The baby was then observed carefully, with heart rate and respiration being monitored. Lumbar punctures were repeated as often as necessary if ventricular width increased by 2 mm or more above the measurement before the first tap. If lumbar puncture yielded no more than 2 ml cerebrospinal fluid, ventricular puncture could be performed. This was carried out through the anterior fontanelle at least 1 cm lateral to the midline, entering the larger lateral ventricle. If repeated taps were necessary for more than four weeks, and head enlargement continued, permanent shunting was discussed, but the decision to insert a shunt also depended on the general condition of the infant, the weight, and the protein concentration in the cerebrospinal fluid.

Conservative management
The appearance on ultrasound scans did not dictate treatment in the group that was managed conservatively. The criteria for removal of cerebrospinal fluid were: (*i*) excessive head enlargement for at least two weeks; namely, an increase in head circumference of twice the normal velocity for gestational age after entry to the trial[15]; or (*ii*) symptomatic raised intracranial pressure with a measured cerebrospinal fluid pressure greater than 1·60 kPa (12 mm Hg) (if a bulging fontanelle and neurological abnormality suggested raised intracranial pressure, a lumbar puncture or ventricular tap could be carried out to measure pressure).

The criteria for permanent shunting were the same in both treatment groups; that is, failure to control head size with no contraindication to shunting—for example, cardiopulmonary disease, infection, or a high concentration of protein in the cerebrospinal fluid.

MONITORING AND COMPLIANCE
In each neonatal unit one neonatologist was responsible for cranial ultrasound scanning (in a few hospitals in conjunction with a radiologist). Before infants were entered into the trial, three meetings of collaborators were held to reach agreement on scanning techniques, measurement of ventricles, and recognition of intraventricular haemorrhage and parenchymal cerebral lesions. A parenchymal lesion was judged to be present if there was persistent echodensity in the cerebral substance viewed in two planes. 'Parenchymal lesion' included both parenchymal 'extension' of periventricular haemorrhage and periventricular leucomalacia. Participants were specifically asked to document the presence or absence of any parenchymal lesions at the time of entry to the trial.

Scanning was usually carried out daily during the first week of life for infants having intensive care, and then weekly while in hospital. After entry to the trial, scanning was performed daily on most infants having early treatment with taps, as the decision to tap depended on whether there had been further ventricular enlargement. In the group managed conservatively scanning did not determine management but was, initially, carried out at least once every three days.

After entry into the trial, recordings were made of head circumference, ventricular width, lumbar and ventricular taps (and volume of cerebrospinal fluid removed), cerebrospinal fluid pressure on the day of entry and subsequently (if it had been measured), and details about the analysis of the cerebrospinal fluid (such as presence of organisms or cells and the protein concentration). Non-communicating post-haemorrhagic ventricular dilatation was defined as the inability to drain more than 2 ml of cerebrospinal fluid by lumbar puncture. The clinical coordinator could be contacted by telephone to clarify difficulties in carrying out the protocol, and he also monitored compliance with the protocol as case records were returned.

STATISTICAL CONSIDERATIONS
Before starting the trial it was estimated that 60 surviving infants in each treatment group would give an 80% chance of detecting a significant (p<0·05) reduction in severe impairments from

50% to 25%. We expected posthaemorrhagic ventricular dilatation to occur in 3–4% of infants of very low birth weight (<1500 g), and to be associated with a death rate of about 20%. The 15 neonatal intensive care units that collaborated admit roughly 1500 very low birthweight infants each year, equivalent to about 45–60 cases of posthaemorrhagic ventricular dilatation annually, so a recruitment period of three years was planned. Analyses have been on the groups as allocated, regardless of subsequent management. There were no interim analyses. Secondary analyses were stratified by whether a parenchymal lesion was recorded on entry to the trial. These investigated, firstly, whether early treatment reduces neuromotor impairment in children without a parenchymal lesion at the onset of treatment and, secondly, whether early treatment limits the extent of impairment other than neuromotor in those children with a pre-exisiting parenchymal lesion.

FOLLOW UP ASSESSMENT OF SURVIVORS AT 12 MONTHS CORRECTED AGE

Surviving children were assessed in their own homes at about one year after their expected date of delivery. All except three were seen by a single developmental paediatrician (Dr L Mutch) who was unaware of their original trial allocation; two Swiss children and one other child were assessed by local paediatricians. The assessment consisted of an interval history, a Griffiths's assessment of development,[16] and a standardised neurological examination as described by Amiel-Tison and Grenier.[17] Vision and hearing were assessed clinically to ensure that the child was able to participate in the developmental assessment, but full assessment of hearing and vision will not be available for all the children until a later age. Where the Griffiths's test was inappropriate because of severe visual deficit, a Reynell-Zinkin test was used to provide an approximate performance for age.[18]

For each child, outcome was summarised in two ways. Firstly, neuromotor signs were described in terms of their distribution and the severity of any motor impairment. Secondly, an overall assessment was made on the basis of all the findings including neurological signs, developmental condition, hearing and vision, health, and degree of alertness and interest, according to the scheme suggested by Amiel-Tison and Stewart.[19] Agreement was reached between the examiner and one of these authors on the classification of all the children based on the results of the examinations. The children were classed in three main groups as follows:

Normal

No neuromotor or neurosensory impairment was detected; Griffiths's developmental quotient was more than 70 and there were no neurobehavioural problems. For the purposes of overall assessment in this study, abnormal head size alone was not a criterion for assignment to an abnormal group.

Neuromotor impairment alone

Impairment was detected, but limited to the neuromotor system. This group was subdivided into those without disability, those with moderate disability, and those with severe disability.

Neuromotor plus other impairments

Multiple impairments were detected, affecting not only the neuromotor system. This group was subdivided into those with visual impairments, those with sensorineural hearing loss, those with developmental quotients of less than 70, and those with a combination of visual, hearing, and developmental impairments. All the children in this group were disabled. The aim of this scheme was to distinguish between impairments resulting from the initial event that preceded the ventricular dilatation, and subsequent impairment. Pre-existing injury is likely to be limited to the periventricular region and cause neuromotor impairment, albeit of variable severity. Raised intraventricular pressure could lead to damage beyond the periventricular region and cause other types of impairment.

Results

A total of 157 infants were enrolled in the trial during the three year period; 79 were allocated to have early treatment and 78 to be managed conservatively. During this period six infants in the collaborating centres who were known to have been eligible for enrolment were not entered, either because the parents did not consent or because the investigator was not available. Thirty infants died between entering the trial and the one year follow up, leaving 66 survivors in the early treatment group and 61 in the group managed conservatively. Three infants in each group could not be followed up because they had moved abroad.

Table 1 shows the characteristics of all the infants entering the trial, and of the 121 who were assessed at 12 months of age. Nearly all were of very low birth weight and there was a preponderance of boys. Randomisation achieved an acceptable balance of important variables between the two groups. Overall, roughly two thirds had parenchymal brain lesions and over 80% had ventriculospinal communication at the time of entry to the trial. There were fewer parenchymal lesions in the group allocated to early drainage of cerebrospinal fluid (59% compared with 71%). More children with parenchymal lesions subsequently died in the group managed conservatively, however, and the groups of survivors assessed at 12 months were similar in this respect (59% compared with 66%). The mean cerebrospinal fluid pressure at entry to the trial, roughly 1·20 kPa (9 mm Hg) in both groups, was three times the mean cerebrospinal fluid pressure in normal neonates, suggesting that most of the infants in this trial had ventricular enlargement caused by increased cerebrospinal fluid pressure.

Table 2 shows details of the early management of ventricular dilatation and confirms that there were pronounced differences in the treatment of the two groups during the early weeks.

Table 1 Description of the groups at entry to trial. Figures are mean (SD) except where otherwise stated

	All randomised		Survivors seen at one year corrected age	
	Early drainage of cerebrospinal fluid (n=79)	Managed conservatively (n=78)	Early drainage of cerebrospinal fluid (n=63)	Managed conservatively (n=58)
No (%) boys	57 (72)	49 (63)	45 (71)	36 (62)
Birth weight (g)	1220 (440)	1245 (436)	1239 (459)	1304 (478)
Gestational age at birth (weeks)	28·3 (2·8)	28·4 (2·9)	28·4 (3·0)	28·8 (3·3)
Age at trial entry (days)	19·1 (11·2)	15·9 (7·3)	19·7 (11·1)	15·6 (7·4)
No (%) with parenchymal brain lesion	47 (59)	55 (71)	37 (59)	38 (66)
No (%) not stated	3 (4)	1 (1)	2 (3)	1 (2)
Type of parenchymal lesion:				
No (%) bilateral	13 (16)	17 (22)	11 (17)	9 (16)
No (%) unilateral	29 (37)	36 (46)	24 (38)	28 (48)
No (%) not stated	5 (6)	2 (3)	2 (3)	1 (2)
Reason for eligibility:				
No (%) with progressive ventricular dilatation from <97th centile to 4 mm more than 97th centile for gestational age	70 (89)	68 (87)	56 (89)	51 (88)
No (%) with clots in ventricle with width >97th centile for gestational age on initial scan	6 (8)	10 (13)	4 (6)	7 (12)
No (%) not stated	3 (4)	0	3 (5)	0
No (%) with ventriculospinal communication	61 (77)	65 (83)	51 (81)	49 (84)
Pressure of cerebrospinal fluid (mm Hg)* (n=102)	9·2 (4·7)	8·9 (5·9)	9·1 (4·8)	8·3 (4·2)
Ventricular width (mm) (n=114)	17·4 (2·1)	17·8 (2·1)	17·4 (2·0)	18·0 (2·1)
Head circumference (cm) (n=122)	28·1 (2·8)	28·8 (3·3)	28·4 (2·9)	29·0 (3·1)

*1 kPa=7·5 mm Hg.

Table 2 Neonatal management of posthaemorrhagic ventricular dilatation by treatment allocation. Figures are given as number (%) except where otherwise stated

	All randomised		Survivors seen at one year corrected age	
	Early drainage of cerebrospinal fluid (n=79)	Managed conservatively (n=78)	Early drainage of cerebrospinal fluid (n=63)	Managed conservatively (n=58)
First 14 days (after day of entry)				
One or more taps	71 (90)	43 (55)	57 (90)	35 (60)
Median No of taps (10th and 90th centiles)	5 (0, 9)	1 (0, 5)	5 (1, 9)	1 (0, 4)
Management:				
Spinal taps only	39 (49)	27 (35)	31 (49)	21 (36)
Ventricular taps only	7 (9)	5 (6)	5 (8)	3 (5)
Spinal and ventricular taps	25 (32)	11 (14)	21 (33)	11 (19)
Median volume of cerebrospinal fluid removed (ml) (10th and 90th centiles)	58 (8, 158)	5 (0, 77)	61 (4, 161)	10 (0, 77)
Mean (SE) change in ventricular width (mm) (n=90)	0·3 (0·5)**	2·5 (0·6)**	0·0 (0·5)**	2·5 (0·6)**
Mean (SE) change in head circumference (cm) (n=122)	1·8 (0·2)*	2·4 (0·1)*	1·9 (0·3)*	2·5 (0·2)*
At 100 days (after day of entry)				
One or more taps	73 (92)	55 (71)	59 (94)	43 (74)
Median No of taps (10th and 90th centiles)	7 (1, 37)	4 (0, 28)	10 (1, 43)	4 (0, 31)
Management:				
Spinal taps only	33 (42)	22 (28)	25 (40)	16 (28)
Ventricular taps only	7 (9)	7 (9)	5 (8)	5 (9)
Spinal and ventricular taps or reservoir	33 (42)	26 (33)	29 (46)	22 (38)
Median volume of cerebrospinal fluid removed (ml) (10th and 90th centiles)	116 (14, 678)	38 (0, 556)	152 (10, 700)	53 (0, 556)
Other aspects				
Ventriculoperitoneal shunt insertion only	41 (52)	42 (54)	39 (62)	36 (62)
Choroid plexus coagulation	2 (3)	3 (4)	2 (3)	3 (5)
Died:				
Before hospital discharge	12 (15)	13 (17)	Not applicable	Not applicable
After discharge but before follow up assessment	1 (1)	4 (5)	Not applicable	Not applicable
Lost to follow up	3 (4)	3 (4)	Not applicable	Not applicable

*p=<0·5, **p=<0·01.

Table 3 Incidence of infection of the cerebrospinal fluid (meningitis or ventriculitis) in infants who had not (yet) had operations for hydrocephalus

Case No	No of lumbar punctures before infection	No of ventricular taps before infection	Organism	Shunt subsequently carried out	Outcome
Group receiving early treatment with taps					
1	11	6	Coagulase negative staphylococcus	Yes	Survived
2	0	3	Yeast*	No	Died
3	4	2	Yeast*	Yes	Survived
4	10	4	Coagulase negative staphylococcus	Yes	Survived
5	0	12	Not identified	No	Died
6	2	0	Yeast*	Yes	Survived
7	15	0	Yeast*	Yes	Survived
Group managed conservatively					
8	0	3	Coagulase negative staphylococcus	Yes	Survived
9	0	10	Enterobacter spp	Yes	Survived
10	2	0	Yeast*	No	Survived
11	7	1	Klebsiella spp	Yes	Survived

*Yeast=Candida albicans or Hansenula anomala.

During the first 14 days after randomisation the early treatment group had a median of five cerebrospinal fluid taps compared with only one tap in the group managed conservatively (usually this was done to exclude meningitis), the volume of cerebrospinal fluid removed in the early treatment group was nearly 12 times greater than in the group treated conservatively, and this was associated with significantly smaller increases in ventricular width and head circumference.

By 100 days after entry many of the conservatively managed group had met the criteria for cerebrospinal fluid drainage, and the differences in management between the two treatment groups were therefore less pronounced. It was common for infants to have ventriculospinal communication at first, which later become non-communicating. Thus half the infants in the early treatment group eventually had one or more ventricular tap.

Infection of the cerebrospinal fluid was common even in infants who had not (yet) had any surgery for hydrocephalus (table 3). Seven infants in the early treatment group (9%) developed ventriculitis (without having had an operation) and two of these died. Four infants in the group managed conservatively (5%) developed ventriculitis (without having had an operation).

Overall, 30 children (19%) died during the first year, 13 (16%) in the early treatment group and 17 (22%) in the group managed conservatively. Of the survivors, 75 (62%) had ventricular shunts inserted, and six (5%) moved abroad and were lost to follow up; there were no differences between the trial groups (table 2). Nor were there clear differences in morbidity during the time between discharge from hospital and the follow up assessment (table 4); about 70% of both groups were readmitted to hospital, many more than once, and often for revision of their shunts.

Table 5 shows Griffiths's developmental scales one year after full term. Quotients could not be measured in 15 children because their vision was too severely impaired; all six such children in the early treatment group, and six of the nine in the group managed conservatively were judged to have developmental delay. Almost half of the survivors scored less than 70 on the Griffiths's locomotor scale, about a third

Table 4 Morbidity between discharge from hospital and follow up assessment. Figures are given as number (%)

	Early drainage of cerebrospinal fluid (n=63)	Managed conservatively (n=58)
Hospital readmission:	44 (70)	40 (69)
1	17 (27)	20 (34)
2	13 (21)	8 (14)
≥3	14 (22)	12 (21)
Admission because of condition of central nervous system	13 (21)	11 (19)
Admission for revision of shunt	18 (29)	16 (28)
Seizures since discharge from hospital	4 (6)	11 (19)
Taking anticonvulsant drugs	5 (8)	8 (14)

Table 5 Assessment of development at follow up (Griffiths's scales). Figures are given as number (%)

	Early drainage of cerebrospinal fluid (n=63)	Managed conservatively (n=58)
Locomotor quotient:		
Not measureable	6 (10)	9 (16)
<50	6 (10)	10 (17)
50–69	17 (27)	16 (28)
70–99	19 (30)	11 (19)
≥100	15 (24)	22 (38)
Social scale quotient:		
Not measureable	6 (10)	9 (16)
<50	3 (5)	2 (3)
50–69	3 (5)	9 (16)
70–99	36 (57)	23 (40)
≥100	15 (24)	15 (26)
Hearing-speech quotient:		
Not measureable	6 (10)	9 (16)
<50	0	1 (2)
50–69	4 (6)	8 (14)
70–99	40 (63)	26 (45)
≥100	13 (21)	14 (24)
Eye-hand coordination quotient:		
Not measureable	6 (10)	9 (16)
<50	3 (5)	7 (12)
50–69	9 (14)	9 (16)
70–99	31 (49)	18 (31)
≥100	14 (22)	15 (26)
Performance quotient:		
Not measureable	6 (10)	9 (16)
<50	4 (6)	9 (16)
50–69	9 (14)	8 (14)
70–99	34 (54)	19 (33)
≥100	10 (16)	13 (22)
General quotient:		
Not measureable	6 (10)	9 (16)
<50	2 (3)	6 (10)
50–69	8 (13)	7 (12)
70–99	35 (56)	23 (40)
≥100	12 (19)	13 (22)

scored less than 70 on the performance and eye-hand coordination scales, and about a quarter scored less than 70 on the personal-social, hearing-speech, and overall scales. Taking into account the developmental assessment of the 15 'blind' children, 16 children in the early treatment group (25%) and 19 children in the group managed conservatively (33%) had developmental delay (relative risk 0·78; 95% confidence interval (CI) 0·44 to 1·36).

As many as 54 children in the early treatment group (86%) and 49 (84%) in the group managed conservatively had abnormal neuromotor signs (relative risk 1·01; 95% CI 0·87 to 1·18); distribution and severity were similar in the two groups (table 6).

Table 7 summarises other measures of physical outcome. Although there were more babies with head circumference less than the 10th centile in the early treatment group, the mean head circumference was similar in the two groups. Visual impairment, nystagmus, and visual field deficits were less common in the early treatment group, but this difference was not significant (relative risk 0·61; 95% CI 0·35 to 1·08). Some of the children may have had retinopathy of prematurity, but this was not ascertained at the time. Overall, 67 out of 118 children tested (57%) could not see a 2 mm diameter object and 40 out of 103 (39%) of those that could see any object, had a squint.

Table 8 shows the results of the developmental paediatrician's overall assessment of out-

Table 6   Neuromotor signs at follow up. Figures are given as number (%)

	Early drainage of cerebrospinal fluid (n=63)		Managed conservatively (n=58)	
	All cases	Severe cases	All cases	Severe cases
Hypertonia affecting four limbs	14 (22)	6 (10)	14 (24)	5 (9)
Hypertonia affecting three limbs	8 (13)	1 (2)	5 (9)	1 (2)
Hypertonia affecting two limbs:				
Ipsilateral	11 (17)	3 (5)	12 (21)	1 (2)
Contralateral	8 (13)	1 (2)	2 (3)	0
Hypertonia affecting one limb	8 (13)	1 (2)	6 (10)	0
Axial imbalance	3 (5)	0	7 (12)	0
No neuromotor abnormality detected	9 (14)	0	9 (16)	0

Table 7   Physical assessment at follow up. Figures are given as number (%) unless otherwise stated

	Early drainage of cerebrospinal fluid (n=63)	Managed conservatively (n=58)
Mean (SE) head circumference (cm)	46·6 (3·8)	46·9 (3·6)
Head circumference centile:		
<10th centile	17 (27)	6 (10)
10–90 centile	26 (41)	33 (57)
>90th centile	20 (32)	19 (33)
Problems with sucking	3 (5)	6 (10)
Problems with choking	16 (25)	16 (28)
Excessive dribbling	6 (10)	10 (17)
Ability to see objects (at 22 cm):		
2 mm (diameter)	28 (44)	23 (40)
3–5 mm	17 (27)	10 (17)
15 mm	8 (13)	7 (12)
25 mm	3 (5)	7 (12)
No vision or sees light only	6 (10)	9 (16)
Not known	1 (2)	2 (3)
Nystagmus	7 (11)	13 (22)
Visual field deficit (but sees object)	4 (6)	7 (12)
No vision or sees light only and nystagmus or visual deficit, or both	14 (22)	21 (36)
Squint (abnormal cover test but sees object)	21 (33)	19 (33)
Distraction (hearing) test:		
Normal	36 (57)	31 (53)
Questionable	20 (32)	20 (34)
Abnormal	6 (10)	5 (9)
Head control insufficient for test	1 (2)	2 (3)

Table 8   Final condition as judged by examiner's overall assessment, or death before assessment. Figures are given as number (%)

	Early drainage of cerebrospinal fluid (n=79)	Managed conservatively (n=78)
No impairment detected	9 (11)	9 (12)
Neuromotor impairment alone:	29 (37)	19 (24)
No disability	9	6
Moderate disability	4	5
Severe disability	16	8
Neuromotor plus other impairment with disability with or without DQ <70:	25 (32)	30 (38)
Neuromotor and visual	8	9
Neuromotor and sensorineural hearing loss	2	1
Neuromotor and DQ <70	4	3
Neuromotor and combination of visual impairment sensorineural hearing loss, and DQ <70	11	17
Died	13 (16)	17 (22)
No follow up assessment	3 (4)	3 (4)

DQ=developmental quotient.

come. This, like all the neurodevelopmental assessments, was carried out without knowledge of the treament allocation. Of those children whose outcome is known (76 and 75, respectively), 58 (76%) in the early treatment group and 60 (80%) in the group managed conservatively had died or were disabled (relative risk 0·95; 95% CI 0·81 to 1·13). Although there was a suggestion of a difference between the treatment groups, with fewer children among survivors in the early treatment group having additional non-neuromotor impairments, this was not significant (relative risk 0·77; 95% CI 0·52 to 1·13). Only 18 of survivors (15%) assessed at 1 year of age were judged to be normal.

Secondary analyses, with patients stratified by whether a parenchymal lesion had been reported to be present at the time of entry to the trial, showed no difference between the trial groups in the incidence of neuromotor signs (table 9). In particular, there was no suggestion of benefit of early treatment among those who did not have parenchymal lesions at the time of entry into the trial. Nearly all the children who had parenchymal lesions at the time of entry into the trial had abnormal neuromotor signs, but there were fewer children in the early treatment group with impairments affecting other systems and this difference is marginally significant (p=0·05; relative risk 0·67; 95% CI 0·45 to 1·00).

Discussion

The poor outcome of children enrolled in the study has confirmed the importance of post-haemorrhagic ventricular dilatation despite its rarity. We recognised that no single unit could mount a sufficiently large trial in a reasonable length of time to evaluate early removal of cerebrospinal fluid by serial tapping. With an unprecedented degree of cooperation among neonatal units in Europe, 15 different neonatal intensive care units agreed on a protocol and enrolled infants in the trial. The planned target of 120 surviving infants was reached successfully; virtually all the infants who met the eligibility criteria were recruited. Random treatment assignment was effective in distributing the main prognostic variables between the two treatment groups (table 1). A 95% follow up at one year, with infants spread over three countries, was satisfactory, and data from the six unassessed infants who had left the country of their birth could not have altered the overall conclusions of the study.

Table 9   Outcome of survivors assessed at follow up, stratified by whether a parenchymal lesion was recorded as present at the time of entry to the trial. Results are given as number (%)

	Parenchymal lesion at time of entry		Others	
	Early drainage of cerebrospinal fluid (n=37)	Managed conservatively (n=38)	Early drainage of cerebrospinal fluid (n=26)	Managed conservatively (n=20)
Neuromotor signs				
Hypertonia affecting four limbs	11 (30)	11 (29)	3 (12)	3 (15)
Hypertonia affecting three limbs	7 (19)	5 (13)	1 (4)	0
Hypertonia affecting two limbs:				
Ipsilateral	10 (27)	11 (29)	1 (4)	1 (5)
Contralateral	2 (5)	3 (8)	8 (31)	2 (10)
Hypertonia affecting one limb	3 (8)	5 (13)	5 (19)	1 (5)
Axial imbalance	2 (5)	3 (8)	1 (4)	4 (20)
No neuromotor abnormality detected	2 (5)	0	7 (27)	9 (45)
Final overall condition				
No impairment detected	2 (5)	0	7 (27)	9 (45)
Neuromotor impairment alone:	18 (49)	12 (32)	11 (42)	7 (35)
No disability	2	4	7	2
Moderate disability	2	3	2	2
Severe disability	14	5	2	3
Neuromotor plus other impairment with disability with or without DQ <70:	17 (46)	26 (68)	8 (31)	4 (20)
Neuromotor and visual	6	7	2	2
Neuromotor and sensorineural hearing loss	0	1	2	0
Neuromotor and DQ <70	1	2	3	1
Neuromotor and combination of visual sensorineural hearing loss and DQ <70	10	16	1	1

DQ=developmental quotient.

Compliance with trial management was generally good, as shown by the differences in the number of taps and amount of cerebrospinal fluid removed during the first 14 days, and the effects of these differences on the pattern of ventricular and head enlargement (table 2). More than half the children in the early treatment group required ventricular taps to maintain the policy. Early drainage of cerebrospinal fluid had no effect on the incidence of shunt insertion subsequently, or on the number of later admissions to hospital, including those for revision of shunts (table 4). Any invasive procedure concerning cerebrospinal fluid has the potential for causing infection. Very low birthweight infants with posthaemorrhagic ventricular dilatation are particularly vulnerable, because of low concentrations of immunoglobins and complement.[20] It is well known that infants who have had shunts inserted for posthaemorrhagic ventricular dilatation have a considerable risk of infection,[13] but it is disturbing to find an appreciable number with infections of the cerebrospinal fluid after lumbar punctures and ventricular taps. Of the 157 infants enrolled, 11 (7%) developed infections of the cerebrospinal fluid before any operation had been carried out. All had had cerebrospinal fluid taps before the infection developed, and it is possible that organisms were introduced into the cerebrospinal fluid at the time of puncture. Two of these infants died with ventriculitis, and all but one of the surviving infected infants later required a permanent shunt. Although there were more infections of the cerebrospinal fluid in the early treatment group the difference was not statistically significant. This could reflect the later use of taps in the group that was managed conservatively. Non-invasive methods for reducing cerebrospinal fluid pressure, such as treatment with acetazolamide,[21] have obvious advantages in respect of the risk of infection. They are, however, of uncertain effectiveness

and safety, and should be evaluated in further randomised controlled trials before widespread introduction into clinical practice.

Of the 121 children who had a follow up assessment, 103 (85%) had abnormal neuromotor signs, and in 28 (23%) hypertonia affected all four limbs (table 6). Early drainage of cerebrospinal fluid had no effect in this respect, regardless of whether or not there was a parenchymal lesion at the time of entry into the trial. There were fewer children with visual impairments and low developmental quotients in the early treatment group (table 7), and these differences were reflected in the smaller number of children who were classified as having impairments of more than just the neuromotor system (table 8). This difference was not statistically significant, however, when the total trial groups were compared.

As expected, the presence of a parenchymal lesion at trial entry was associated with a poorer long term outcome and nearly all these children had neuromotor impairments (table 9).[22] The difference in the pattern of disability between the total randomised groups seems to be limited to children with pre-existing parenchymal lesions (table 9). Children with severe motor disability, in particular, were less likely to have other types of impairment if they were in the early treatment group. Such secondary analyses should be interpreted cautiously because they are prone to wide statistical fluctuations and the observed difference is only small.[23] Nevertheless, the findings are consistent with the hypothesis that early treatment of infants with pre-existing parenchymal lesions would have little, if any, effect on motor impairment because this would reflect pre-existing periventricular damage, but would reduce other types of impairment by limiting the extent of any extension of injury to other areas of the brain.

The study provided no evidence that early treatment prevents impairments in children

who do not have parenchymal lesions at the start of treatment (table 9). What is more, the overall rate of disability (46%) among these children was higher than expected.[22] In part this may be explained by the method used for diagnosis of the brain lesions. Ultrasound detects parenchymal haemorrhagic lesions accurately in the early days of life. These lesions, which are often due to secondary venous infarction, are fairly localised and are believed to lead to predominently neuromotor sequellae. By contrast, the sensitivity of detection of periventricular leucomalacia by ultrasound is low (29%),[24] and the lesions may only be recognised later. There may be multiple lesions and the type of sequellae at follow up will depend upon the site and extent of the lesions. Thus in this study periventricular leucomalacia may not have been detected until after trial entry or even missed. This explanation is supported by the identification of parenchymal lesions after trial entry in seven (15%) children and by the type of impairments found at follow up (see table 9). Nevertheless, on the basis of the findings of this study, early treatment in children who do not have parenchymal lesions at the start of treatment, does not seem to be warranted in view of the possible adverse effects of repeated drainage of the cerebrospinal fluid.

Pending the results of a further review of surviving children at the age of 2·5 years (which will include assessment of language and perception), early and repeated drainage of cerebrospinal fluid should be considered for infants with posthaemorrhagic ventricular dilatation who already have parenchymal lesions. If such management is chosen, cerebrospinal fluid taps should be performed with great care because of the risks of infection.

Ventriculomegaly Trial Group
Professor R Cooke, Dr J Rennie, Dr M Weindling, Liverpool Maternity Hospital; Dr A Whitelaw, clinical coordinator, Hammersmith Hospital, London; Dr A Stewart, neurodevelopmental follow up consultant, Dr P Hope, Dr P Hamilton, Professor O Reynolds, University College Hospital, London; Dr A Wilkinson, Dr M Rochefort, John Radcliffe Hospital, Oxford; Dr G Gandy, Dr C Morley, Rosie Maternity Hospital, Cambridge; Dr E Hey, Professor J Parkin, Princess Mary Maternity Hospital, Newcastle; Dr D Harvey, Queen Charlotte's Maternity Hospital, London; Dr D Milligan, Newcastle General Hospital; Dr R Pearce, Dr M Smith, Dr J Bridson, Jessop Hospital for Women, Sheffield; Dr E Griffin, Coombe Lying-in Hospital, Dublin; Professor G Duc, Kinderspital, Zurich; Dr T Lissauer, Dr R Rivers, St Mary's Hospital, London; Dr M Drayton, Dr P Fleming, Dr B Speidel, Professor P Dunn, Southmead Hospital, Bristol, and Bristol Maternity Hospital; Dr W Gorman, Dr N O'Brien, National Maternity Hospital, Dublin; and Dr A Grant, Mrs S Hunt, central coordinator, Dr L Mutch, neurodevelopmental follow up, Ms H Ashurst, computer anlaysis, National Perinatal Epidemiology Unit, Oxford).

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