Phase 1 Trial of Prevention of Hydrocephalus After Intraventricular Hemorrhage in Newborn Infants by Drainage, Irrigation, and Fibrinolytic Therapy

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ABSTRACT. *Objective.* **Treatment of posthemorrhagic ventricular dilation in premature infants is fraught with failures and complications. We have piloted a new treatment aimed at removing intraventricular blood and the cytokines associated with hydrocephalus.**

Methods. **Twenty-four infants were enrolled with ventricular width enlarged to 4 mm over the 97th centile after a large intraventricular hemorrhage. Sixteen had parenchymal brain lesions before treatment. Median gestation was 28 weeks, and birth weight was 1150 g. At a median postnatal age of 17 days, 2 ventricular catheters (1 right frontal, 1 left occipital) were inserted with 13 infants also having a reservoir frontally. Tissue plasminogen activator 0.5 mg/kg was given intraventricularly 8 hours before the ventricles were irrigated with artificial cerebrospinal fluid at 20 mL/h for a median of 72 hours.**

Results. **Seventeen of 23 survivors (74%) did not require a ventriculoperitoneal shunt. One infant (of 23 weeks' gestation) died. Two infants developed reservoir-associated infection, and 2 infants had a second intraventricular hemorrhage. Of the 19 survivors aged >12 months postterm, 8 were normal, 7 (37%) had single disability, and 4 (21%) had multiple disabilities.**

Conclusions. **Shunt surgery was reduced compared with historical controls with similar treatment criteria. Mortality and single and multiple disability rates all showed downward trends. Reducing pressure, free iron, and proinflammatory and profibrotic cytokines may reduce periventricular brain damage and permanent hydrocephalus. Additional advances will require a controlled trial and better knowledge of the mechanisms of hydrocephalus.** *Pediatrics* **2003;111:759–765;** ***hydrocephalus, intraventricular hemorrhage, newborn infant, irrigation, fibrinolysis.***

ABBREVIATIONS. IVH, intraventricular hemorrhage; PHVD, posthemorrhagic ventricular dilation; CSF, cerebrospinal fluid; tPA, tissue plasminogen activator; TGF-β, transforming growth factor-β; DRIFT, drainage, irrigation, and fibrinolytic therapy.

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Hemorrhage into the ventricles of the brain is 1 of the most serious complications of premature birth despite improvements in the survival of premature infants. Large intraventricular hemorrhage (IVH) has a high risk of neurologic disability, and >50% of these children go on to develop progressive ventricular dilation.[1] Murphy et al[2] provided evidence that posthemorrhagic ventricular dilation (PHVD) in the 1990s had a more aggressive course than previously with appreciable mortality and morbidity in extremely premature infants. Treatment is much more difficult than other types of hydrocephalus because the large amount of blood in the ventricle combined with the small size and instability of the patient make an early ventriculoperitoneal shunt operation impossible. A period of repeated lumbar or ventricular reservoir tapping may be followed after many weeks by shunt surgery. There is a considerable complication rate from such surgery, and the child is permanently dependent on the shunt system. Treatment by repeated lumbar or ventricular tapping and the use of acetazolamide and furosemide to reduce cerebrospinal fluid (CSF) production do not reduce the need for shunt surgery, do not improve neurologic outcome, and have appreciable adverse effects.[3,4]

We have documented that tissue plasminogen activator (tPA)[5] and fibrin degradation products[6] are present in posthemorrhagic CSF, but we have also demonstrated that plasminogen concentrations are very low[7] and plasminogen activator inhibitor-1 is present in high concentrations.[8] Phase 1 clinical trials of intraventricular fibrinolytic therapy treatment[9–11] and a small randomized trial[12] have not given encouraging results when intraventricular fibrinolytic therapy is started 2 to 4 weeks after the IVH, by which time the infant is already developing hydrocephalus.

Multiple blood clots may obstruct the ventricular system or channels of reabsorption initially but lead to a chronic arachnoiditis of the basal cisterns involving deposition of extracellular matrix proteins in the foramina of the fourth ventricle and the subarachnoid space.[13] Transforming growth factor-β (TGF-β) is likely to be a key mediator of this process as TGF-β is involved in the initiation of wound healing and fibrosis.[14] TGF-β elevates the expression of genes encoding fibronectin, various types of collagen,[15,16] and other extracellular matrix components.[17]

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TGF-β is elevated in the CSF of adults with hydrocephalus after subarachnoid hemorrhage, and intrathecal administration of TGF-β to mice resulted in hydrocephalus.[18,19] We have demonstrated that CSF from infants with PHVD has TGF-β concentrations that are 10 to 20 times those of nonhemorrhagic CSF and that the concentration of TGF-β in CSF is predictive of later shunt surgery.[20] Intraventricular blood may have adverse effects on the immature periventricular white matter by a variety of mechanisms, including elevated CSF pressure,[21] free radical generation facilitated by free iron,[22] and inflammation.[23]

Adults with IVH have been treated by early ventricular drainage combined with intraventricular recombinant tPA.[24–27] The most recent published study[27] describes 20 adult patients with IVH and impaired consciousness or coma. In 9 patients, hemorrhage was from a ruptured aneurysm, in 5 there was hypertensive brain hemorrhage, in 4 there was arteriovenous malformation, and in 2 the cause was unknown. Continuous ventricular external drainage was established through a frontal approach. Two to 5 mg of tPA was injected via the ventricle, and the drain was then clamped for 2 hours. The ventricular catheter was then opened to drain with no resistance. The intraventricular tPA was repeated every 24 hours until there was a reduction in hematoma size and the third and fourth ventricles were clear of blood on computed tomography scan. The ventriculostomy drain was removed after a mean duration of 23 days. One died, and 11 of the 20 eventually needed a ventriculoperitoneal shunt. All 4 of the anecdotal reports of intraventricular fibrinolytic therapy in adults have described mortality much lower than historical controls (eg, 5% vs 60%–91%).

Clearly, IVH in adults is very different from IVH in premature infants with respect to cause and also likelihood of raised intracranial pressure, but the adult experience and our previous research on this topic suggested that early drainage together with intraventricular fibrinolytic therapy should be tried in premature infants with large IVH. To try to remove as much blood and cytokine as possible, we have combined this treatment approach with irrigation of the ventricular system with a protein-free artificial CSF. This article reports a phase 1 trial involving 24 infants.

METHODS

Infants were included when they were of at least 23 weeks' gestation, were <3 months of age, and had IVH documented on ultrasound (Fig 1a) followed by enlargement of ventricular width on each side to 4 mm over the 97th centile[28] (Fig 1b) or midline shift indicating pressure. All of the infants of gestational age <34 weeks were identified by routine cerebral ultrasound scanning started within the first 24 hours and repeated twice weekly for 4 weeks or until discharge if the scans had not normalized. Infants of 34 weeks' gestation or greater presented with neurologic signs and were then scanned by ultrasound. Scanning was repeated twice weekly when there was an abnormality on ultrasound or persistent neurologic signs. Signed informed parental consent was obtained. Infants were excluded when they had a prothrombin time >20 seconds or platelets <50 000/mm^3.

The end points of this study were need for permanent ventricular shunt, infection in the central nervous system, mechanical problems with the drainage catheter, second intraventricular bleeding during treatment, or death. Neurologic outcomes were motor disability, cognitive disability, hearing loss, visual loss, and epilepsy

Ventricular Access Surgery

One of 2 procedures was used depending on the infant's stability:

1. The infant was taken to the operating theater, and, under general anesthesia, a ventricular reservoir was inserted into the front of 1 lateral ventricle and an external ventricular drain was inserted into the back of the contralateral ventricle.
2. If the infant was considered too unstable for transfer to the operating room or an operating room was not available, intravenous anesthesia was achieved with morphine 0.4 mg/kg and pancuronium 0.1 mg/kg in the neonatal intensive care unit, under a radiant heater. A size 5 umbilical artery catheter was inserted, via the anterior fontanelle into the front of 1 lateral ventricle, and a size 6 side hole feeding tube was inserted, via the lambdoid suture, into the occipital horn of the other ventricle (Fig 2).

Irrigation and tPA Administration

After 1 to 2 hours of postoperative stabilization, 0.5 mg/kg human recombinant tPA (Actilyse; Boehringer Ingelheim International, Ingelheim, Germany) was injected via the reservoir or anterior ventricular catheter into the cerebral ventricles and left for 8 hours before irrigation started. A Codman external ventricular drainage system (Johnson & Johnson, Piscataway, NJ) was connected (Fig 2). This is a closed system that allows sampling and up to 70 mL to be collected in a small reservoir held on a level with the infant's head. Below this is a larger collecting bag that can take 500 mL.

Artificial CSF (Torbay Pharmaceuticals Manufacturing, Paignton, United Kingdom) contains 148 mmol/L sodium, 4.02 mmol/L potassium, 1.22 mmol/L magnesium, 1.36 mmol/L calcium, 133.8 mmol/L chloride, 0.58 mmol/L phosphate, 1.22 mmol/L sulfate, and 22 mmol/L bicarbonate. Vancomycin 10 mg and intrathecal gentamicin 5 mg were added to each bottle. This was infused at 20 mL/h through a filter into the ventricular reservoir (or anterior ventricular catheter if there was no reservoir). The drainage reservoir was set initially to be at the same level as the center of the head.

CSF Pressure

A pressure transducer was connected via a 3-way tap to the input line (Fig 2). This was carefully zeroed to the center of the infant's head. The value was displayed continuously on the monitor with the alarm set to sound if the intracranial pressure exceeded 6 mmHg. The volumes of fluid infused and drained were measured and written down every 30 minutes. The height of the drainage catheter was lowered or raised to maintain the output of fluid greater than the input and the intracranial pressure below 7 mmHg. When the rate of drainage decreased despite this, the infusion was stopped and the cause was investigated. A sample of drainage fluid was taken every day for protein, bacteriology, and microscopy.

Discontinuing Irrigation

Irrigation was normally conducted for 72 hours but could be continued for up to 1 week if the CSF had not cleared from the appearance of cola to that of white wine. The drainage catheter was then removed as was the frontal catheter when there was no ventricular reservoir. The ventricular reservoir was left in place. The combination of drainage, irrigation, and fibrinolytic therapy was given the acronym DRIFT.

Criteria for Shunt Surgery

When progressive enlargement of the ventricles and head occurred after DRIFT, a ventricular reservoir was inserted (if 1 was not already in place). Ventricular reservoir taps (10–20 mL/kg) were conducted when symptomatic intracranial hypertension was suspected or there was an increase in head circumference of ≥2 mm per day. Ventriculoperitoneal shunting was conducted when there was persistent need for tapping or there was persistent accelerated head enlargement. Additional requirements for shunt

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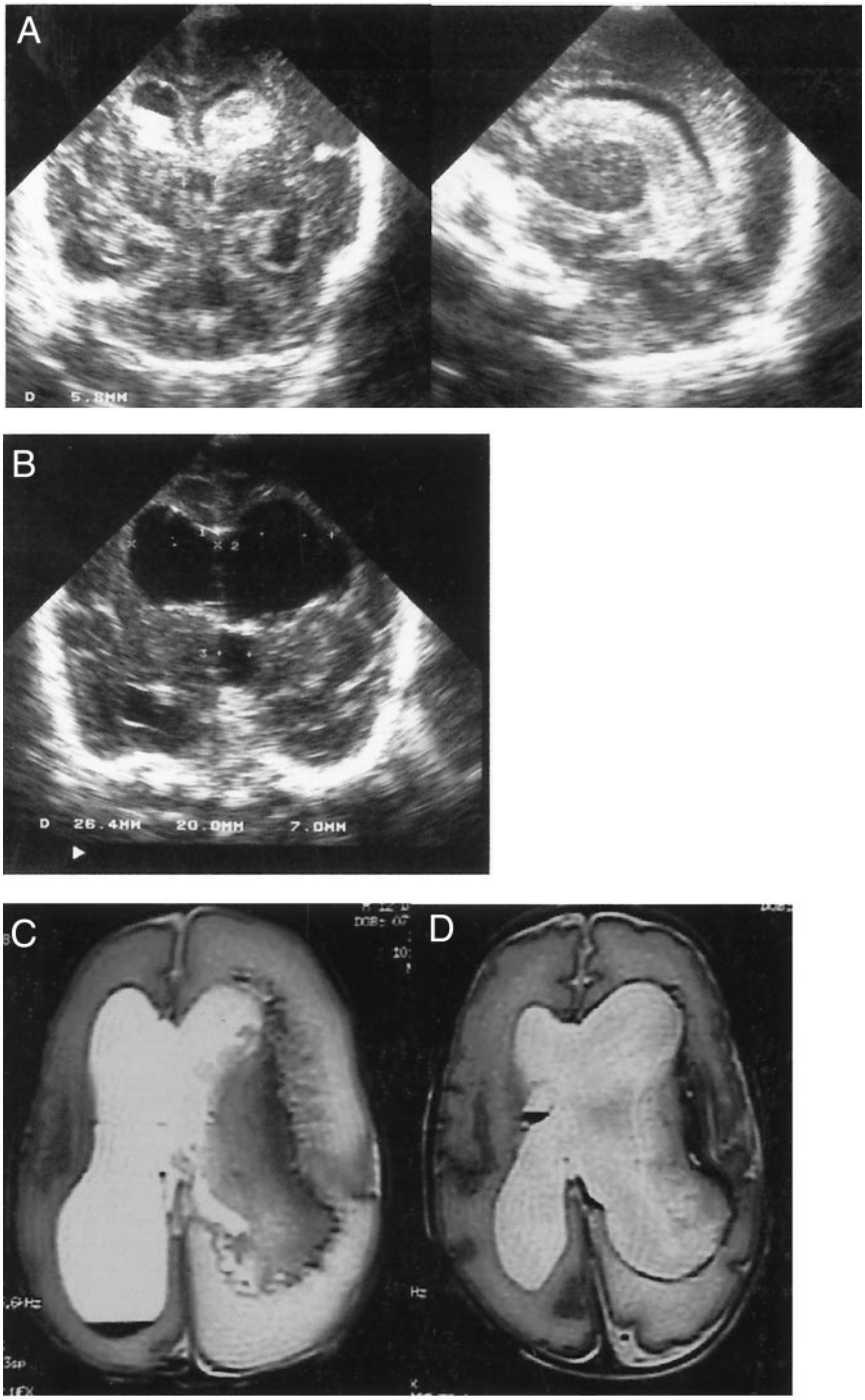

Fig 1. Cerebral ultrasound scans showing extensive intraventricular clot (white) before administration of TPA (midcoronal and parasagittal views; a), measurement of width of the lateral ventricles and third ventricle (coronal; b). Cerebral magnetic resonance images (T2 weighted): c, IVH (dark) and with ventricular dilation (white). There is considerable edema (white) in the parenchyma of the left hemisphere. d, Clearing of intraventricular blood after DRIFT and reduction in edema in the left hemisphere.

surgery were freedom from infection and CSF protein ≤1.5 g/L. No strict weight limit was set, but the infants were usually >2500 g when shunted.

Neurologic Follow-up

Contact was maintained with all of the surviving infants, and all but 1 survivor have been examined in Bristol. Because detection of disability under 12 months may be unreliable, we report here only neurologic outcomes for all 19 surviving children older than 12 months postterm at a median age of 2.5 years postterm (range: 13 months–4 years). One family moved to the other side of the country, and we have relied on reports from the local developmental pediatrician. All of the other surviving children have had developmental assessments by a pediatrician, motor assessments by a physical therapist, and formal audiology on 2 or more occasions. Ascertainment of cognitive disability was based on the nonmotor Ruth Griffiths Scales of Infant Development.[29] An overall assessment as to single or multiple disability was made as described by Amiel-Tison and Stewart.[30]

A certificate for the use of Actilyse outside of the registered indications had been obtained from the Medicines Control Agency (London), and this project was approved by the Research Ethics Committees of North Bristol NHS Trust and United Bristol Healthcare Trust.

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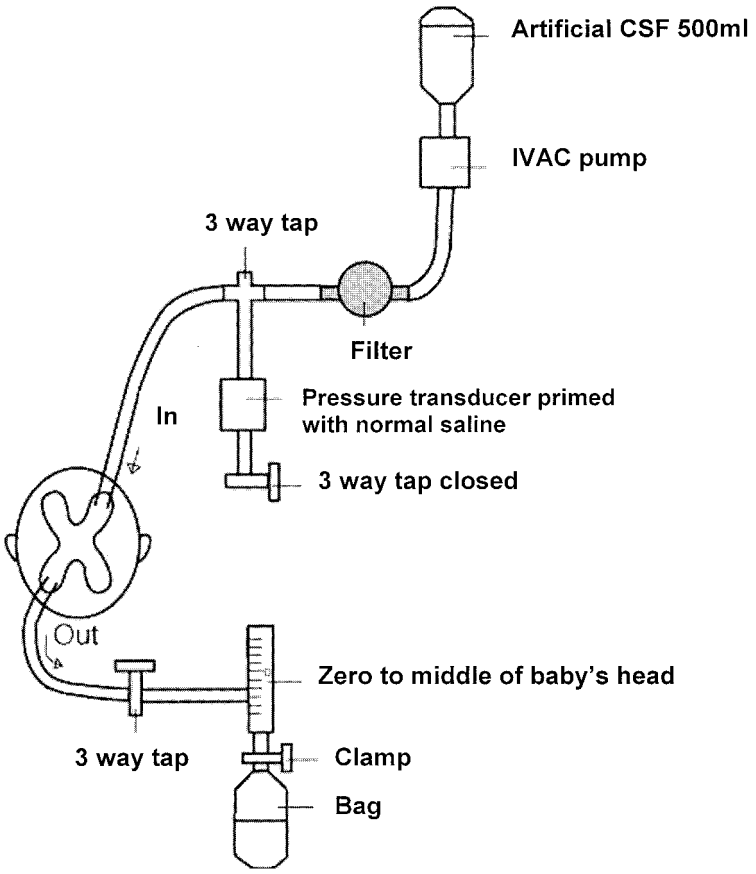

Fig 2. The direction of irrigation and drainage of the ventricular system during DRIFT.

RESULTS

Between May 1998 and April 2002, 24 infants met the inclusion criteria in the 2 regional neonatal intensive care units in Bristol. This corresponds to ~1 infant for every 4000 births in our catchment area. All of the parents who were given written and verbal information gave consent to DRIFT. Median gestational age was 28 weeks (range: 23–42 weeks), and median birth weight was 1150 g (range: 760–3770 g). Median age of starting treatment was 17 days (range: 3–28 days). In all cases, a large (grade 3) IVH filled the majority of the cavity in at least 1 lateral ventricle, and the third ventricle was dilated. In 16 of 24, there were parenchymal periventricular echodensities or echolucencies indicative of hemorrhagic infarction or periventricular leukomalacia noted before any intervention. Median ventricular width was 16 mm (range: 14–22 mm) on the right and 16 mm (range: 14–19 mm) on the left. In 2 cases, the combined ventricular width was 39 mm with an obvious shift of the midline. In 13 cases, a ventricular reservoir and a ventricular drain were inserted. In 11 cases, 2 ventricular catheters were inserted with no reservoir because the infant's unstable condition precluded transfer to the operating room or no operating room was available. Two infants were irrigated for 2 days, 11 for 3 days, 3 for 4 days, 4 for 5 days, 2 for 6 days, and 2 for 7 days. The duration of irrigation depended on how slowly the drainage fluid had cleared. Intravenous morphine (5–40 μg/kg/h) was used as sedation, and 18 of 24 infants were mechanically ventilated throughout the irrigation procedure. The total amount of protein removed by drainage varied from a maximum of 6 g in the first 24 hours to a minimum of 0.15 g in the last 24 hours (median: 0.7 g/24 h).

Outcomes

Major short-term and medium-term outcomes are summarized in Table 1.

Second IVH

The median change in hemoglobin during irrigation was −2.35 g/dL (range: 1.7 g/dL to −6.3 g/dL). Sixteen infants received transfusion of red cells during the DRIFT procedure because of the fall in hemoglobin. Two infants had a definite second IVH. One infant became pale and started having abnormal "boxing" and "cycling" movements, confirmed as electrical seizures. Cranial ultrasound showed that the lateral ventricles had become filled with echodense material. The hemoglobin fell by 6.3 g/dL. Tranexamic acid 10 mg (plasmin inhibitor) was given intravenously, drainage was continued to maintain normal intracranial pressure and remove blood, and packed red cells were transfused. The second infant hemorrhaged after a rapid decompression of the ventricles but stabilized without tranexamic acid.

Infection in the Central Nervous System

There was a mild leukocytosis in the CSF during irrigation in 6 cases but no positive bacteriology. Two infants with ventricular reservoirs in place began to leak through the suture line, and after several

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TABLE 1. Clinical Details and Short-Term and Long-Term Morbidity in Infants Treated for PHVD With DRIFT

Birth Weight (Grams)	Gestation (Weeks)	Left Parenchymal Lesion	Right Parenchymal Lesion	Infection	Second IVH	VP Shunt	Hearing Loss	Visual Loss	Neuromotor Function	Epilepsy	Cognitive Disabilty
1225	27	No	Yes	No	No	Yes	No	No	Right hemiplegia	No	Yes
1960	30	No	Yes	No	No	No	No	No	Left hemiplegia	No	No
1790	31	No	Yes	No	No	No	No	No	Left hemiplegia	No	No
760	24	No	Yes	Yes	No	Yes	Yes	No	Left hemiplegia	Yes	Yes
876	26	No	Yes	No	No	No	No	No	Left hemiplegia	No	No
1120	28	Yes	Yes	No	No	No	No	No	Balance problems	No	No
3770	39	Yes	No	No	No	No	No	No	Normal	No	No
1080	27	No	Yes	No	Yes	Yes	Yes	No	Normal	No	No
2010	34	Yes	No	No	No	No	No	No	Normal	No	No
1005	28	No	Yes	No	No	Yes	No	No	Normal	No	No
1090	26	Yes	No	No	No	No	No	No	Normal	No	No
1180	27	Yes	Yes	No	No	No	No	Yes	Diplegia	No	Yes
2644	41	Yes	Yes	No	No	No	No	No	Diplegia	No	Yes
1320	29	Yes	Yes	No	No	No	No	No	Diplegia	No	No
780	23	Yes	Yes	No	No	No	Dead	Dead	Dead	Dead	Dead
2000	33	No	No	No	No	No	No	No	Normal	No	No
980	27	No	No	No	No	No	No	No	Normal	No	No
1280	29	No	No	No	No	No	No	No	Normal	No	No
1100	27	No	No	No	No	Yes	Yes	No	Normal	No	No
855	26	No	No	Yes	No	Yes	No	No	Normal	No	No
904	27	No	No	No	No	No	No	No	Under 12 mo		
3720	42	No	No	No	No	No	No	No	Under 12 mo		
2115	33	No	No	No	No	No	No	No	Under 12 mo		
815	29	Yes	No	No	Yes	No	No	No	Under 12 mo		

VP indicates ventriculoperitoneal.

weeks coagulase-negative staphylococci were cultured from the CSF. Both of these infants later required ventriculoperitoneal shunt operations.

Catheter Blockage

In 1 case, multiple blockages in the ventricular catheters developed and made it impossible to achieve irrigation. After 6 hours, 0.25 mg/kg tPA was injected into each ventricular catheter. The blockages cleared, and subsequent drainage and irrigation proceeded without difficulty.

Mortality

The only infant who died was born at 23 weeks and 6 days and developed respiratory distress syndrome, hypotension, coagulopathy, pulmonary hemorrhage, and patent ductus arteriosus, in addition to a large IVH with some periventricular echodensities and progressive ventricular dilation. DRIFT was conducted for 72 hours. The infant remained unresponsive after sedation was stopped, and electroencephalogram showed very low amplitude. There was no evidence of secondary bleeding or infection, and intensive care was withdrawn.

Need for Permanent Ventricular Shunt

Six (26%) of the 23 surviving infants have required ventriculoperitoneal shunt surgery. Of the 23 surviving infants without a shunt, median head circumferences centile is 50 (range: 0.4–99)

Neurologic Development

This section is restricted to the 19 surviving infants aged >12 months postterm (Table 1). Of the 5 infants with no parenchymal brain lesions at entry, all 5 have normal motor development. One of the 5 infants has a partial hearing loss. None of these infants has cognitive disability, visual loss, or epilepsy.

Of the 14 surviving infants with parenchymal brain lesions before treatment, 5 have normal motor development and 1 of these has partial sensorineural hearing loss without motor disability. Five have hemiparesis contralateral to the parenchymal lesion including 1 infant with hemiparesis, cognitive disability, and epilepsy well-controlled on medication. One infant with a parenchymal lesion has balance problems without spasticity.

Three infants with bilateral parenchymal lesions that subsequently became cystic leukomalacia have spastic diplegia, and 2 of 3 have cognitive disability. One of these had delayed visual development. Overall, 11 (58%) of 19 survivors developed disability including 4 (21%) with multiple disabilities.

DISCUSSION

Study Design

DRIFT is a radical new intervention that was piloted because PHVD had no treatment that was effective and safe. As the treatment is highly invasive and technically demanding, it was essential to have a phase 1 trial in which the feasibility and obvious practical challenges were addressed. There is also a learning curve when new procedures are introduced. It was not appropriate to begin with a randomized controlled trial until we were sure that the technique could be used consistently and safely by our staff.

Need to Remove Blood

The treatment was based on the principle of trying to reduce pressure and edema, and remove as much old blood and TGF-β as possible from the CSF space (Fig 1c and d). We have previously documented in 2

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infants that DRIFT was followed by lower concentrations of TGF-β1 in the CSF.[22] Blood is the most likely source of the release of TGF-β1 into the CSF because the cytokine is stored in platelets. Recent data showing the presence of free iron and proinflammatory cytokines in posthemorrhagic CSF provide 2 additional reasons for irrigating and draining the CSF space.[16,17]

Timing of Treatment and Criteria for Treatment

The timing of the intervention was difficult because 1) early intervention probably increases the risk of rebleeding as the bleeding site has not been repaired surgically, 2) early intervention risks the possibility that one is intervening in infants who would not develop hydrocephalus and did not need intervention, and 3) late intervention ensures that one has identified the true hydrocephalus cases but the pathology may be irrevocably decided with no chance of the intervention altering the course. We elected to use treatment criteria similar to the previous large trials of treatment of PHVD and thus selected infants with a high risk of shunt dependence and disability. This allowed us to compare our outcomes with historical controls, acknowledging the limitations of such comparisons.

Adverse Effects

Infection

DRIFT treatment is highly invasive, and 2 cases of CSF infection occurred, as well as 1 clinically significant secondary hemorrhage. The 2 infections both occurred many days after reservoir insertion and leakage from suture lines. None of the infants who had only ventricular catheters became infected. The use of therapeutic concentrations of gentamicin and vancomycin in the irrigation fluid may have helped to prevent infection. Our rate of CNS infection was 8%, which compares with 14% in the PHVD drug trial.[4]

Hemorrhage

Two infants developed clinically evident second IVH that required treatment. Over the whole group, the median drop in hemoglobin of 2.35 g/dL over 3 to 7 days could be because some of the infants had subclinical intraventricular bleeding during DRIFT, or it could just be the result of repeated blood sampling necessary for intensive care. Small secondary bleeding would not be entirely surprising as tPA had been injected into a ventricular system with recent catheter insertion and a recent bleeding site. Diagnosing small secondary IVH is not easy as the drainage fluid is blood stained to start with and liquid blood is not echogenic.

Pressure and Electrolytes

The use of continuous intracranial pressure measurement on the input line was very important as it provided the earliest warning of obstruction in the system and was the only really reliable way of knowing whether appropriate amounts of fluid were being drained. For maintaining intracranial pressure below 7 mmHg, it was necessary to remove more fluid than was pumped in. This is because of the infant's endogenous production of CSF. Because each infant was running a CSF deficit of approximately 100 mL/d, there was a considerable loss of sodium that had to be replaced to maintain a normal plasma sodium.

Demands on Nursing Resources

The need to maintain careful observation of the infant, sterile technique, gentleness to avoid pain and secondary bleeding, very accurate CSF balance, and continuous intracranial pressure monitoring for 72 or more hours in addition to the normal demands of intensive care of a small preterm infant placed a heavy responsibility on our nursing staff. The additional work could, perhaps, be compared with having an infant on hemofiltration. DRIFT required one-to-one nursing, and there were times when infants who were suitable for DRIFT could not be admitted because of inadequate nursing staffing.

Improved Outcomes

Mortality in our series was 4%, compared with 17% in the PHVD drug trial[4] and 19% in the ventriculomegaly trial,[3] 2 large series with similar entry criteria. Death or shunt was 29% in our series, significantly lower than 67% in the ventriculomegaly trial[3] ($P = 0.0006$ by χ^2) and 58% in the PHVD trial[4] ($P = 0.014$ by χ^2). The shunt surgery rate was 26% in survivors, lower than 62% in the ventriculomegaly trial ($P = 0.01$ by χ^2)[3,4] and 57% in the PHVD drug trial ($P = 0.011$ by χ^2). A recent series by de Vries et al[31] described 42 infants with PHVD in whom intervention was considered after the ventricular width had reached the same criterion. Sixty-two percent of the infants eventually received ventriculoperitoneal shunts despite the use of lumbar punctures and/or reservoirs in some cases.[31] Neurodevelopmental outcome shows a trend toward DRIFT decreasing disability. Seventy-three percent of infants in the ventriculomegaly trial and 73% of infants in the PHVD trial had disability,[3,4] whereas in our series, 58% had disability. Of the infants in the ventriculomegaly trial, 51% had multiple disabilities,[2] and in the PHVD drug trial, 39% had multiple disability. Twenty-one percent of the infants in our series had multiple disabilities. The study of PHVD by de Vries et al[31] excluded infants with parenchymal hemorrhagic infarction and found a 26% disability rate. All 5 infants without parenchymal brain lesions in our study show no signs of cerebral palsy and have developmental quotients above 85.

Our preliminary findings are on relatively small numbers and lack contemporaneous controls, and some children may reveal more disability as they get older. Nevertheless, it is biologically plausible that drainage and irrigation may reduce ongoing brain injury by normalizing pressure, reducing free radical injury from non–protein-bound iron, and reducing inflammatory cytokines. Although the figures show a reduction in shunt dependence with trends toward reducing mortality and disability in favor of DRIFT, it is also clear that DRIFT fails to prevent shunt

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dependence in some cases. This may be because it is impossible to remove enough blood clot from the ventricular system or because the intervention was used too late to prevent TGF-β–stimulated fibrosis. Additional work is needed on the role of TGF-β and other cytokines in the pathogenesis of posthemorrhagic hydrocephalus with a view to molecularly based interventions. This will require experimental modeling of PHVD. One purpose of this preliminary report now is to encourage potential collaborators in a multicenter, randomized trial of DRIFT versus conventional treatment to contact the corresponding author: andrew.whitelaw@bristol.ac.uk. The DRIFT trial is described at: http://www.neonatalneurology.org.uk

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