NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of drainage, irrigation and fibrinolytic therapy (DRIFT) for post-haemorrhagic hydrocephalus in preterm infants

Treating bleeding-related progressive enlargement of the head in babies born prematurely by drainage, irrigation and breaking down blood clots

Bleeding in the brain is a serious complication in babies born prematurely. It can result in obstruction of the flow of fluid (called cerebrospinal fluid [CSF]) within the cavities of the brain leading to progressive enlargement of the head (hydrocephalus). Death or permanent brain damage may follow.

There are very few treatments for this condition. This procedure aims to remove the blockage and reduce its harmful effects by draining excess CSF from the brain, washing out the blood, and breaking down blood clots using drugs (fibrinolytics).

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2010.

Procedure name

Drainage, irrigation and fibrinolytic therapy (DRIFT) for post-haemorrhagic hydrocephalus in preterm infants.

Specialty societies

- Society of British Neurological Surgeons
- British Association of Perinatal Medicine.

Description

Indications and current treatment

Intraventricular haemorrhage is a serious complication occurring within a few days of birth in a small proportion of preterm infants; it is more common and severe in very preterm infants born before thirty weeks of gestation. In some infants, intraventricular haemorrhage can be fatal. Among those surviving, some will develop post-haemorrhagic dilatation of the ventricles followed by progressive enlargement of the head, also known as hydrocephalus. In those infants, hydrocephalus is thought to be the result of permanent damage (caused by the bleed) to intraventricular structures responsible for cerebrospinal fluid (CSF) drainage and absorption.

Once established, hydrocephalus causes progressive dilatation of the head circumference and is associated with different degrees of neuro-developmental disability.

Standard management of hydrocephalus typically involves repeated drainage of CSF (through repeated lumbar punctures, or repeated tapping of a surgically inserted ventricular access device – or reservoir) followed by insertion of a ventriculo-peritoneal (V-P) shunt a few weeks or months later. Several revisions of the shunt may be required, either because of infection or blockage.

In preterm infants, shunt insertion is only possible a few weeks or months after birth. CSF drainage or use of diuretics (to decrease CSF production) is sometimes used before shunt insertion can be considered; however, no treatment has been proven to reduce the need for shunt surgery or improve neurological outcomes.

What the procedure involves

This procedure is used with the aim of minimising the risk of death, the risk of progression of hydrocephalus, and the need for shunt insertion. It aims to do this by reducing intracerebral pressure, washing out excess blood and potentially toxic substances (e.g. cytokines and free radicals).

The procedure is performed with the infant under general anaesthesia in a specialised neonatal intensive care unit. Two catheters are inserted into the lateral ventricles from right frontal to left occipital or vice versa. A fibrinolytic agent is given intraventricularly with the aim of lysing thrombi in the ventricles; after 8 hours, ventricular lavage is started. Artificial CSF is inserted through the frontal catheter (typically at a flow rate of 20 ml/h). Fluid is drained through the occipital catheter to a closed drainage system. Outflow is adjusted so that it exceeds inflow, aiming for intracranial pressure readings of less than 7 mm Hg. Lavage continues until the colour of the drained fluid becomes normal (‘cola to white wine’), typically within 3 days. The catheters are then removed.

Tools for assessing development

Bayley Scales of Infant Development includes scales assessing mental development and psychomotor development. Each scale gives a composite score: the Mental Development Index and Psychomotor Development Index, respectively.

Ruth Griffiths Scales of Infant Development has 5 subscales on locomotor, personal/social, speech and hearing, eye-hand coordination, and performance and a composite score is calculated.

The standardised mean of each composite score is 100, with a standard deviation of 15. Scores between 85 and 115 are considered to be within the normal range.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to drainage, irrigation and fibrinolytic therapy (DRIFT) for post-haemorrhagic hydrocephalus in preterm infants. Searches were conducted of the following databases, covering the period from their commencement to 26 July 2011: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Preterm infants with post-haemorrhagic hydrocephalus.
Intervention/test	Drainage, irrigation and fibrinolytic therapy (DRIFT).
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on about 101 infants from 1 randomised controlled trial (RCT) (2 publications from this trial) and 1 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on drainage, irrigation and fibrinolytic therapy (DRIFT) for post-haemorrhagic hydrocephalus in preterm infants

Abbreviations used: CI, confidence interval; CSF, cerebrospinal fluid; DRIFT, drainage, irrigation, and fibrinolytic therapy; IVH, intraventricular haemorrhage; MDI, mental development index; OR, odds ratio; PDI, psychomotor development index; rTPA, recombinant tissue plasminogen activator; SD, standard deviation; tPA, tissue plasminogen activator

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Whitelaw A (2010)[1]

RCT
UK, Poland, Norway (4 centres)
Recruitment period: 2003–6
Study population: preterm infants (< 27 weeks' gestation) with post-haemorrhagic ventricular dilatation
n = 77 (39 DRIFT vs 38 standard treatment)
Median gestation: 27 weeks vs 28 weeks
Median birth weight: 1050 vs 1130 g
Sex: 74% vs 63% male

Patient selection criteria: intraventricular haemorrhage on ultrasound scan, no more than 28 days old, progressive dilatation of both lateral ventricles, each having: width greater than 4 mm over 97th centile, 4 mm anterior horn diagonal (1 mm over 97th centile), 26 mm thalamo-occipital distance (1 mm over 97th centile), 3 mm third ventricle width (1 mm over 97th centile) (if infant had measurements above any of these values on one side combined with an obvious midline shift, this was considered a pressure effect and the infant was eligible).</td>
<td>Number of infants analysed: 77 (39 DRIFT vs 38 standard treatment)

Mortality at 2-year follow-up
<table>
<tr><th>Treatment group</th><th>Mortality rate</th></tr>
<tr><td>DRIFT</td><td>7.7% (3/39)</td></tr>
<tr><td>Standard treatment</td><td>13.2% (5/38)</td></tr>
</table>
(rate calculated by analyst; timing of deaths and causes not reported)

Severe disability at 2-year follow-up
<table>
<tr><th></th><th>DRIFT n (%)</th><th>Standard treatment n (%)</th><th>OR (95% CI)</th><th>Adjusted OR (95% CI)*</th></tr>
<tr><td>Severe disability **</td><td>18 (46)</td><td>22 (57.9)</td><td colspan="2">Not reported</td></tr>
<tr><td>Severe disability or death</td><td>21 (53.8)</td><td>27 (71)</td><td>0.48 (0.19–1.22)</td><td>0.25 (0.08–0.82)</td></tr>
</table>
(p values not reported), *adjusted for gender, birth weight and grade of IV; **percentage calculated by analyst

Cognitive disability considered severe if MDI score < 55 (when MDI < 70 defined cognitive impairment, the differences were not significant).
Sensorimotor disability considered severe if including any of the following: inability to walk without assistance, sit without support, control head without support, use hands to feed self</td>
<td>Secondary IVH
Recruitment for this trial was stopped early because of excess intraventricular bleeding in the intervention group (see entry of earlier publication from this study for details[2]).

When recruitment was resumed (see 'comments' column), 1 of the 7 infants recruited had secondary IVH (in the DRIFT group) so recruitment was stopped again.

There were no significant differences between the proportions of those with MDI < 55 or with severe sensorimotor disability between those with and without secondary IVH.</td>
<td>Follow-up issues:
• None lost to follow-up.

Study design issues:
• All preterm infants requiring intensive care or showing neurological abnormalities at centres were screened.
• Computer-generated randomisation stratified according to study centre in blocks of 8, 10 or 12.
• Assessor of development was blind to initial treatment allocation.
• If infants in DRIFT group had persistent enlargement of ventricles and excessive head growth, they received standard treatment and ventricular reservoir (but infants did not cross from standard into DRIFT group).
• Shunting indicated if excessive head growth (confirmed not to be brain growth on</td>
</tr>
</table>

Abbreviations used: CI, confidence interval; CSF, cerebrospinal fluid; DRIFT, drainage, irrigation, and fibrinolytic therapy; IVH, intraventricular haemorrhage; MDI, mental development index; OR, odds ratio; PDI, psychomotor development index; rTPA, recombinant tissue plasminogen activator; SD, standard deviation; tPA, tissue plasminogen activator

Study details	Key efficacy findings	Key safety findings	Comments
Exclusion criteria: prothrombin time > 20 s, partial thromboplastin time > 50, platelet count < 50,000/ml. Technique: Intervention – drainage, irrigation and fibrinolytic therapy (with rTPA); Standard treatment – no active treatment unless excessive head enlargement (2 mm/day) or suspicion of raised intracranial pressure then lumbar puncture removing 10 ml/kg but if 2 or more punctures did not drain enough to equalise head growth, a ventricular reservoir was given. Follow-up: **2 years** Conflict of interest/source of funding: none	or communicate by speech; or blindness/only light perception, or hearing loss uncorrected by hearing aid. ***Need for ventriculo-peritoneal shunt*** **Treatment group** | **% with shunt** DRIFT | 41.0% (16/39) Standard treatment | 39.5% (15/38) (percentages calculated by analyst) ***Effect on Bayley Development Indices (version 2) at mean 25 months (SD 1.7)*** **DRIFT (n = 35) n (%)** | **Standard treatment (n = 32) n (%)** | **OR (95% CI)** | **Adjusted OR (95% CI)*** MDI ≥ 85 | 8 (23) | 9 (28) | 0.31 (0.11–0.86) p = 0.024 | 0.17 (0.05–0.57) p = 0.004 70–84 | 9 (26) | 3 (9) 55–69 | 7 (20) | 1 (3) < 55** | 11 (31) | 19 (59) PDI ≥ 85 | 4 (12) | 5 (16) | 0.54 (0.20–1.45) p = 0.22 | 0.21 (0.05–0.85) p = 0.028 70–84 | 5 (15) | 5 (16) 55–69 | 11 (32) | 4 (13) < 55 | 14 (41) | 18 (56) *adjusted for gender, birth weight and grade of IVH **< 55 was considered severe cognitive disability (median MDI in DRIFT group was 68 vs < 50 in the standard treatment group)		ultrasound) increased by 2 mm/day after reservoir taps were stopped (when weight reached 2500 g and CSF protein fell to < 1.5 g/l). • Intention-to-treat analyses. • After the trial was stopped early (see explanation below[2]), the Bristol centre was permitted to resume recruitment with tightened vigilance reducing risk of secondary bleeding. However, after 7 infants were included, additional recruitment was stopped because of secondary IVH in 1 treated with DRIFT (authors attributed this to use of rTPA for fibrinolytic therapy). **Study population issues**: • Infants in intervention group had higher proportion of boys, parenchymal infarctions (grade IV IVH; 51 vs 47%), and slightly lower

Abbreviations used: CI, confidence interval; CSF, cerebrospinal fluid; DRIFT, drainage, irrigation, and fibrinolytic therapy; IVH, intraventricular haemorrhage; MDI, mental development index; OR, odds ratio; PDI, psychomotor development index; rTPA, recombinant tissue plasminogen activator; SD, standard deviation; tPA, tissue plasminogen activator

Study details	Key efficacy findings	Key safety findings	Comments
	Effect on components of severe sensorimotor disability (in respect of gait, sitting, hand control, head control, speech, vision, and hearing) and seizures at 2 years		birth weight and gestational age.

Severe disability component	DRIFT (n = 36) n (%)	Standard treatment (n = 33) n (%)
Unable to walk without assistance[a]	16 (44)	17 (52)
Unable to sit[b]	4 (11)	7 (21)
Inability to use hands to feed[c]	4 (11)	4 (12)
Needs support to control head[d]	1 (3)	4 (12)
No communication by speech or system[e]	5 (14)	9 (27)
Blind or perceives light only[f]	2 (6)	4 (12)
Uncorrected hearing loss[g]	0 (0)	2 (6)
Seizures [h]	4 (11)	5 (15)
Severe sensorimotor disability [i]	16 (44)	18 (55)

p value for comparison between groups (two-tailed Fisher's exact test): [a] 0.56, [b] 0.25, [c] > 0.99, [d] 0.19, [e] 0.06, [f] 0.42, [g] 0.23, [h] 0.73, [i] 0.40

A number of other comparisons in outcomes related to the same elements of sensorimotor disability but which were not considered to be a severe disability were also reported in the study. The comparisons favoured the intervention group, but no significance values are reported in the publication.

Abbreviations used: CI, confidence interval; CSF, cerebrospinal fluid; DRIFT, drainage, irrigation, and fibrinolytic therapy; IVH, intraventricular haemorrhage; MDI, mental development index; OR, odds ratio; PDI, psychomotor development index; rTPA, recombinant tissue plasminogen activator; SD, standard deviation; tPA, tissue plasminogen activator

Study details

Whitelaw A (2007)[2]

RCT (earlier publication from above study)

UK

Recruitment period: 2003–6

Study population: preterm infants (< 27 weeks' gestation) with post-haemorrhagic ventricular dilatation

n = **70 (34 DRIFT vs 36 standard treatment)**

Median gestation: 27 vs 28 weeks
Median birth weight: 1066 vs 1079g
Sex: 71% vs 64% male

Patient selection criteria: as described above[1]

Technique: as described above[1]

Follow-up: **until infants were 6 months of age (or discharge, whichever was later)**

Conflict of interest/source of funding: none.

Key efficacy findings

Number of infants analysed: **70 (34 DRIFT vs 36 standard treatment)**

Outcomes at 6 months or discharge (whichever was later)

Outcome	DRIFT n (%)	Standard treatment n (%)	% Difference (95% CI)	Relative risk (95% CI)
Ventriculo-peritoneal shunt	13 (38)	14 (39)*	–1 (–23 to 22)	0.98 (0.54 to 1.78)
Dead	2 (6)	5 (14)	–8 (–22 to 6)	0.42 (0.09 to 2.04)
Dead or shunt	15 (44)	18 (50)	–6 (–29 to 17)	0.88 (0.54 to 1.45)
Secondary reservoir	13 (38)	27 (75)	–37 (–58 to –15)	0.51 (0.32 to 0.81)
Dead or shunt by centre:				
Bristol	8/22 (36)	14/25 (56)	–20 (–48 to 8)	0.65 (0.34 to 1.25)
Katowice	6/10 (60)	4/10 (40)	20 (–23 to 63)	1.5 (0.60 to 3.74)
Glasgow	1/1	0/1	-	-
Bergen	0/1	-	-	-

*1 dead

Infants in the standard group were almost twice as likely to have a ventricular reservoir inserted (38 vs 75%, p = 0.004).

Of those in the standard group, 56% (15/27) of those who received a reservoir later required a shunt.

In the DRIFT group, 6/21 who did not receive a reservoir eventually needed a shunt (reservoir was avoided because of repeated lumbar punctures or enlargement was late enough for shunt surgery to be possible).

Key safety findings

Secondary IVH

(on ultrasound appearance of new intraventricular echodensities within 1 week of randomisation and combined with a fall in haemoglobin of at least 2 g/dl in 2 days)

DRIFT	Standard treatment	p value
35% (12/34)	8% (3/36)	0.014

(most occurred within 24 hours of catheter insertion)

Only 1 patient had clinically apparent IVH (he acutely developed thrombocytopenia).

67% (8/12) of those in the DRIFT group with secondary IVH required shunt surgery, compared with 23% (5/22) of those without secondary IVH (p = 0.032).

Requirement for blood transfusion

Blood transfusions were often required.

	DRIFT	Standard treatment	p value
Mean number required in the first 7 days after randomisation	1.7 (range: 0–4)	0.8 (range: 0–2)	< 0.001

Of those treated with DRIFT:

	With secondary IVH	Without secondary IVH	p value
Mean number required in	2.2 (range:	1.4 (range: 0–	0.012

Comments

Follow-up issues: None lost to follow-up.

Study design issues:

- First publication from RCT described above.
- 47 infants in Bristol, 20 in Katowice, 2 in Glasgow and 1 in Bergen
- Primary outcome was a composite of ventriculo-peritoneal shunt surgery and death.
- Power calculations with 5% level of significance, 60 infants were needed in each group to give 91% power of detecting a reduction from 60% to 30% in primary outcome and 79% power of detecting reduction from 55% to 30%.These were not met.
- Trial was stopped early after 50% of target recruitment because of 1) low likelihood of primary short-term outcome reaching significance and 2) excess secondary IVH in the intervention group.

Study population issues:

- As described above, infants in intervention group had higher proportion of boys, parenchymal infarctions (grade IV IVH; 53 vs 50%), and slightly lower birth weight and gestational age.

Abbreviations used: CI, confidence interval; CSF, cerebrospinal fluid; DRIFT, drainage, irrigation, and fibrinolytic therapy; IVH, intraventricular haemorrhage; MDI, mental development index; OR, odds ratio; PDI, psychomotor development index; rTPA, recombinant tissue plasminogen activator; SD, standard deviation; tPA, tissue plasminogen activator

Study details	Key efficacy findings	Key safety findings	Comments
Whitelaw A (2003)[3] **Case series** UK Recruitment period: 1998–2002 Study population: premature infants with post-haemorrhagic ventricular dilatation n = **24** Median gestation: 28 weeks (range: 23–42) Median age at starting treatment: 17 days (range: 3–28) Median birth weight: 1150 g (range: 760–3770) Sex: not reported Patient selection criteria: less than 3 months of age, IVH on ultrasound followed by enlargement of ventricular width on each side to 4 mm over the 97th centile or midline shift indicating pressure. Exclusion criteria: prothrombin time >20 s, platelet count < 50,000/mm^3. Technique: DRIFT (with 0.5 mg/kg of rTPA) Follow-up: **not reported** Conflict of interest/source of funding:	Number of infants analysed: **24** ***Mortality*** A neonate (< 24 weeks) with multiple organ failure and large IVH treated by the procedure died – there was no evidence of secondary bleeding or infection. ***Need for permanent ventricular shunt*** 26% (6/23) of the surviving infants have required ventriculo-peritoneal shunt surgery. (median head circumferences centile is 50, range: 0.4–99) ***Death or shunt rate:*** 29% (7/24) ***Neurological development (of 19 surviving infants > 12 months post-term)*** Overall, 58% (11/19) developed disability including 21% (4/19) with multiple disabilities. Of the 5 with no parenchymal brain lesions at entry: – all had normal motor development. – 1 had partial hearing loss – none had cognitive disability, visual loss or epilepsy. Of the 14 with parenchymal brain lesions at entry: – 5 have normal motor development and 1 of these has partial sensorineural hearing loss without motor disability – 5 have hemiparesis, cognitive disability and epilepsy well-controlled on medication. – 1 had balance problems without spasticity – 3 with bilateral parenchymal lesions that subsequently became cystic leukomalacia have spastic diplegia and 2 have cognitive disability, one had delayed visual development	***Requirement for blood transfusion*** 16 required transfusion or red cells during the procedure because of a fall in haemoglobin. ***Secondary IVH*** 2 infants were believed to have developed clinically significant secondary IVH – in 1, treatment with intravenous tranexamic acid and pack red cell transfusion was required. ***Secondary infection*** There was mild leukocytosis in the CSF during irrigation in 6 cases but without positive bacteriology. 2 with ventricular reservoirs in place began to leak through the suture line several weeks later. Coagulase-negative *Staphylococci* were cultured from the CSF. ***Catheter blockage*** A patient had multiple blockages in the ventricular catheters, making irrigation impossible. 0.25 mg/kg tPA was injected into each catheter resulting in the resumption of drainage and irrigation without difficulty.	**Follow-up issues**: • None lost to follow-up. **Study design issues**: • This is the pilot study. • Infants were identified with 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 normalised. • Neurological outcomes were reported for those over 12 months post-term as these measures may be unreliable in younger infants. • Developmental assessment was by a paediatrician, motor assessments by a physical therapist and formal audiology on 2 or more occasions (one who had moved was assessed by a local developmental paediatrician). • Cognitive disability was determined from non-motor Ruth Griffiths Scales of Infant Development. • Irrigation was median 3

Abbreviations used: CI, confidence interval; CSF, cerebrospinal fluid; DRIFT, drainage, irrigation, and fibrinolytic therapy; IVH, intraventricular haemorrhage; MDI, mental development index; OR, odds ratio; PDI, psychomotor development index; rTPA, recombinant tissue plasminogen activator; SD, standard deviation; tPA, tissue plasminogen activator			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
supported by a grant from Action Research and a grant from Champions of Child Health.			days (range: 2–7). **Study population issues**: • 16 had parenchymal periventricular echodensities or echolucencies indicative of haemorrhagic infarction or periventricular leukomalacia before treatment.

Efficacy

Death

An RCT of 34 infants treated with drainage, irrigation and fibrinolytic therapy (DRIFT) compared with 36 treated with standard treatment reported that DRIFT did not reduce mortality rates in infants with post-haemorrhagic ventricular dilatation at follow-up to 6 months of age or duration of hospital stay (whichever was longer) (relative risk [RR] 0.42, 95% confidence interval [CI] 0.09 to 2.04)[2].

A second publication with 2-year results from the same RCT, including an additional 7 infants, reported a mortality rate of 8% (3/39) of those treated with DRIFT compared with 13% (5/38) in those treated with standard treatment (timing of death and significance of difference not reported)[1].

Need for shunt insertion

The RCT of 34 infants treated with DRIFT compared with 36 treated with standard treatment reported that DRIFT did not reduce the use of shunt surgery in infants with post-haemorrhagic ventricular dilatation with follow-up to 6 months of age or discharge (whichever was longer) (RR 0.98, 95% CI 0.54 to 1.78)[2].

The later publication from the same RCT reported that a permanent shunt was required in 41% (16/39) of those treated with DRIFT and 40% (15/38) treated with standard treatment within the 2 years of follow-up (timing not reported)[1].

The case series of 24 infants reported that 26% (6/23) of the surviving infants required ventriculo-peritoneal shunt surgery (follow-up not reported)[3].

Neurodevelopmental disability

The later publication of the RCT reported on mental and psychomotor infant development using the Bayley Scales of Infant Development II (BSIDII; range: 0 to 100; greater scores indicating better outcome; mental development index score < 55 was considered to represent severe cognitive disability). Infants treated with DRIFT had significantly lower odds of having a severe cognitive disability (crude odds ratio [OR] 0.31, 95% CI 0.11 to 0.86, p = 0.024) at mean follow-up of 25 months. When the OR was adjusted for gender, birth weight, and grade of IVH, infants treated with DRIFT still had significantly lower odds of having a severe cognitive disability (adjusted OR 0.17, 95% CI 0.05 to 0.57)[1].

Infants treated with DRIFT had lower odds of having a severe psychomotor disability at mean follow-up of 25 months, but this was not significant (psychomotor development index score < 55 was considered to represent severe psychomotor disability; crude OR 0.54, 95% CI 0.20 to 1.40, p = 0.22). When the OR was adjusted for gender, birth weight, and IVH grade, infants treated with DRIFT had significantly lower odds of having a severe psychomotor disability (adjusted OR 0.21, 95% CI 0.05 to 0.85, p = 0.028)[1].

The same study reported on further components of severe sensorimotor disability, assessed at 2 years. Severe disability in respect of gait, sitting, hand control, speech, vision, hearing and seizures was less common in those treated with DRIFT but this was not statistically significant[1]. A number of other comparisons in outcomes related to the same elements of sensorimotor disability but which were not considered to be a severe disability were also reported in the study. The comparisons favoured the intervention group, but no significance values are reported in the publication.

The case series of 24 infants reported that 58% (11/19) of those who were greater than 12 months post-term developed disability, including 21% (4/19) with multiple disabilities (assessment of cognitive disability was said to be based on the Ruth Griffiths Scales of Infant Development but scores were not reported)[3].

Safety

Secondary IVH

The RCT of 34 infants treated with DRIFT compared with 36 treated with standard treatment diagnosed secondary IVH on the basis of ultrasound appearance of echodensities within 1 week of randomisation combined with a fall in haemoglobin of 2 g/dl in 2 days. The study reported secondary IVH occurred in 35% (12/34) of infants treated with DRIFT compared with 8% (3/36) treated with standard treatment ($p = 0.014$). Secondary IVH was asymptomatic in all but 1 infant who developed acute thrombocytopenia[2].

The RCT of 70 patients treated by DRIFT or standard treatment was stopped early after 50% of target recruitment, partly because of the excess secondary IVH in the intervention group[2]. When the trial was resumed at 1 centre with tightened vigilance to reduce the risk of secondary bleeding, an additional 7 were recruited. However, when 1 of these additional infants treated with DRIFT developed secondary IVH, recruitment was again stopped[1].

The case series of 24 infants reported clinically significant secondary IVH in 2 infants. One was successfully treated with intravenous tranexamic acid and the other stabilised without treatment (timing not reported)[3].

Requirement for blood transfusions

The RCT of 34 infants treated with DRIFT compared with 36 treated with standard treatment reported that the mean number of blood transfusions required in the first 7 days after randomisation was 1.7 (range: 0–4) in the DRIFT group and 0.8 (range: 0–2) in the standard group ($p < 0.001$). In the DRIFT group, mean number received was 2.2 (range: 1–4) in those with secondary IVH and 1.4 (range: 0–4) without secondary IVH ($p = 0.012$)[2].

The case series of 24 infants reported that 16 infants required transfusion of blood or packed red cells during the procedure because of a fall in haemoglobin[3].

Infection

The RCT of 34 infants treated with DRIFT compared with 36 treated with standard treatment reported that secondary infection (positive culture of bacteria and raised white cell count in CSF) occurred in 1 infant treated with standard treatment (coagulase-negative *Staphylococci* in an infant with a reservoir)[2].

The case series of 24 infants reported mild leukocytosis in the CSF during irrigation in 6 cases but there was no positive bacteriology. The same case series reported that 2 infants with ventricular reservoirs began to leak through the suture line several weeks later. Coagulase-negative *Staphylococci* were cultured from the CSF[3].

Validity and generalisability of the studies

- All relevant studies include a number of the same main authors: 2 publications from 1 RCT and the preliminary feasibility study.
- The RCT was stopped after 50% of target recruitment (as described above) and, as a result, the power of the study was diminished. Planned recruitment required 60 infants in each group to give a 91% power of detecting a reduction from 60% to 30% or a 79% power of detecting reduction from 55% to 30% in the primary outcome (composite of shunt surgery and death).
- The occurrence of IVH is significant as it can counteract the removal of blood which is the intention of this procedure.
- Maximum follow-up is 2 years, which may be too young to assess cognitive function reliably.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

There is currently no NICE guidance related to this procedure.

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr Richard Tubman, Dr Mark Ashton and Professor Andrew Whitelaw (British Association of Perinatal Medicine), Dr Jessica Ternier and Mr Ian Pople (Society of British Neurological Surgeons).

- Four of the Specialist Advisers consider this procedure novel and of uncertain efficacy and safety. One Specialist Adviser states that ventricular lavage has been used for a variety of indications, but DRIFT is novel because an intraventicular fibrinolytic is used, and patients are very small and critically ill.
- Two of the Specialist Advisers perform this procedure regularly. One has performed it at least once, and two have never performed the procedure.
- The comparator is close observation of growth of head circumference and ventricular size on ultrasound, followed by either intermittent drainage of CSF or ventriculo-peritoneal shunt insertion.
- Adverse events in the published literature or from own experience: further intraventricular bleeds, secondary bleeds after TPA administration.
- Theoretical adverse events include infection, meningitis, haemorrhage, displacement of catheters, blockage of catheters, trauma to brain or failure of the procedure.
- Key efficacy outcomes include reduction in the need for a ventriculo-peritoneal shunt and improved cognitive and motor development in the long term.
- One Specialist Adviser was concerned that the procedure does not appear to reduce the need for shunting, though it may improve cognitive outcome.
- One Specialist Adviser stated that this procedure will never be widely practised due to small patient numbers (100–200 annually).
- Training and facilities: the procedure is technically difficult and a neurosurgeon/neonatologists with specific training to place catheters, neonatal intensive care and experienced paediatric neurosurgeon are required. Nurses carrying out DRIFT need to be adequately trained and supervised. Safe transport of the premature infant to the operating theatre is also required.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- Please see comments in 'validity and generalisability of the studies'.

References

1. Whitelaw A, Jary S, Kmita G et al. (2010) Randomized trial of drainage, irrigation and fibrinolytic therapy for premature infants with posthemorrhagic ventricular dilatation: developmental outcome at 2 years. Pediatrics 125: e852–8.

2. Whitelaw A, Evans D, Carter M et al. (2007) Randomized clinical trial of prevention of hydrocephalus after intraventricular hemorrhage in preterm infants: brain-washing versus tapping fluid. Pediatrics 119: e1071–8.

3. Whitelaw A, Pople I, Cherian S et al. (2003) Phase 1 trial of prevention of hydrocephalus after intraventricular hemorrhage in newborn infants by drainage, irrigation, and fibrinolytic therapy. Pediatrics 111: t–65.

Appendix A: Additional papers on drainage, irrigation and fibrinolytic therapy (DRIFT) for post-haemorrhagic hydrocephalus in preterm infants

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Whitelaw A, Cherian S, Thoresen M et al. (2004) Posthaemorrhagic ventricular dilatation: new mechanisms and new treatment. Acta Paediatrica Supplement 93: 11-14.	Narrative review but includes some information on patients treated n = 25	96% (24/25) survival 6 required ventriculo-peritoneal shunt surgery. 2 developed CSF infections and 2 developed secondary intraventricular haemorrhage.	24 of the patients are included in a study in table 2[3].

Appendix B: Related NICE guidance for drainage, irrigation and fibrinolytic therapy (DRIFT) for post-haemorrhagic hydrocephalus in preterm infants

There is currently no NICE guidance related to this procedure.

Appendix C: Literature search for drainage, irrigation and fibrinolytic therapy (DRIFT) for post-haemorrhagic hydrocephalus in preterm infants

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	22/03/2011	March, 2011
Database of Abstracts of Reviews of Effects – DARE (CRD website)	22/03/2011	NA
HTA database (CRD website)	22/03/2011	NA
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	22/03/2011	March, 2011
MEDLINE (Ovid)	22/03/2011	1948 to March Week 2 2011
MEDLINE In-Process (Ovid)	22/03/2011	March 22, 2011
EMBASE (Ovid)	22/03/2011	1980 to 2011 Week 11
CINAHL (NLH Search 2.0 or EBSCOhost)	22/03/2011	NA
BLIC (Dialog DataStar)	22/03/2011	NA

Trial sources searched on 17/03/2011

- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov
- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database

Websites searched on 17/03/2011

- National Institute for Health and Clinical Excellence (NICE)
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference search
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	infant, newborn/ or infant, low birth weight/ or infant, premature/
2	((premat* or preterm or pre term) adj3 (infant* or baby or babies)).tw.
3	(neonat* or newborn*).tw.
4	1 or 2 or 3

5	exp Hydrocephalus/
6	Cerebral Ventricles/
7	Cerebral Ventriculitis/
8	hydrocep*.tw.
9	PHVD.tw.
10	exp Cerebral Hemorrhage/
11	((cerebr* or intraventric*) adj3 h?emorrhag*).tw.
12	(post adj1 (h?emorrhag* or posth?emorrhag*) adj1 ventric* adj1 dilat*).tw.
13	((enlarge* or dilat*) adj3 ventric*).tw.
14	Ventriculomegaly.tw.
15	or/5-14
16	4 and 15
17	(Ventric* adj3 lavag*).tw.
18	(Intraventric* adj3 lavag*).tw.
19	(fibrinoly* adj3 (therap* or treat*)).tw.
20	(drain* or irrigat* or wash*).tw.
21	DRIFT.tw.
22	Drainage/
23	Thrombolytic Therapy/
24	Therapeutic Irrigation/
25	or/17-24
26	16 and 25
27	animals/ not humans/
28	26 not 27