

Ten-year follow-up of a randomised trial of drainage, irrigation and fibrinolytic therapy (DRIFT) in infants with post-haemorrhagic ventricular dilatation

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Scientific summary

Drainage, irrigation and fibrinolytic therapy

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Scientific summary

Background

Severe intraventricular haemorrhage (IVH) with post-haemorrhagic ventricular dilatation (PHVD) is a serious neurological complication seen in preterm infants, with significant neurodisability in survivors. No medical intervention has been proven to reduce neurodevelopmental disability in infants with PHVD.

Objectives

Our primary hypothesis was that drainage, irrigation and fibrinolytic therapy (DRIFT) will reduce severe cognitive disability in children assessed at school age.

Our secondary hypotheses were that DRIFT will:

- improve cerebral visual dysfunction
- improve sensorimotor ability
- improve education outcomes
- improve emotional/behavioural difficulties
- improve preference-based measures of health-related quality of life (HRQoL)
- reduce the health, social care and broader societal costs at 10-year follow-up.

The aims of this study were to:

1. compare cognitive function, visual function, sensorimotor ability and emotional well-being between the two treatment groups in the DRIFT trial at school age
2. explore the use of specialist health/rehabilitative and educational services
3. estimate the economic cost and outcomes of the DRIFT intervention by age 11 years and model longer-term costs and outcomes
4. assess ventricular dilatation and neurosurgical sequelae in the two treatment groups by clinical neuroimaging.

Methods

Design

This was a long-term follow-up study of a multicentre randomised controlled trial set in neonatal intensive care units in Bristol (UK), Katowice (Poland), Glasgow (UK) and Bergen (Norway).

Participants

The children, now aged 10 years, had been randomised to the DRIFT trial as preterm infants and all had suffered a severe degree of PHVD. A small feasibility study preceded the follow-up study, in which all assessments were tested for suitability in the children. The families and children assisted in designing the follow-up study to suit their needs and requirements.

Sample size

In total, 77 children were randomised to the DRIFT trial during 2003–6, of whom 69 survived until age 2 years. Based on a similar effect size documented with severe cognitive disability at age 2 years, a two-group continuity corrected chi-squared test with a 5% two-sided significance level had 80% power

to detect the difference in severe cognitive disability between a control group proportion of 59% and an odds ratio (OR) of 0.17 (i.e. an intervention proportion of 19.7%) when the sample size in each group is 28. With 60 infants (30 in each group), the power was 97% (with an alpha of 5%) to detect a mean cognitive difference of one standard deviation (SD) (commonly 15 points) between the DRIFT and standard treatment groups. It was anticipated that 45 UK children would be assessed in Bristol and 15 Polish children in Katowice, assuming a 90% follow-up rate. Those from Bergen and Glasgow would be sought if numbers were proving difficult to achieve.

Primary outcome

The primary outcome was cognitive disability at school age, expressed as a cognitive quotient (CQ). The British Ability Scales version three was used for children with a developmental age of ≥ 3 years. For children below this threshold, the Bayley Scales of Infant and Toddler Development version three was administered. The final scores were in the format of a cognitive developmental quotient (0 to 100+).

Secondary outcomes

- Cerebral visual function: parent-reported visual ability and parent-completed cerebral visual impairment (CVI) questionnaire.
- Sensorimotor disability: children were assessed using the Movement Assessment Battery for Children-2 (Movement ABC). Severity and numbers with cerebral palsy (CP) were also compared.
- Emotional/behavioural function: parent-completed Strengths and Difficulties Questionnaire (SDQ).
- Parent-reported education outcomes.
- Neurosurgical sequelae on structural brain magnetic resonance imaging (MRI).
- Preference-based measures of HRQoL: parents completed two generic measures of their child's HRQoL at 10-year follow-up, using the Health Utilities Index – 3 (HUI3) and the EuroQol-5 Dimensions, five-level version (EQ-5D-5L).
- Costs of initial hospitalisation and treatment during the neonatal period (including emergency transportation, periods of intensive care and readmissions based on hospital data in the Bristol cohort).
- Costs of subsequent health care in childhood (based on hospital data from the Bristol cohort).
- Health and social care costs and impact on family at 10-year follow-up (based on parent recall).
- Decision analysis model: a simple decision analytical model to estimate the cost-effectiveness of DRIFT compared with standard care from birth to age 18 years. The primary perspective was that of NHS and Personal Social Services in accordance with National Institute for Health and Care Excellence (NICE) guidance. In secondary analysis, we broaden the perspective to include education costs.

Research ethics

Ethics approval was granted by the NHS Health Research Authority (14/SW/1078).

Results

Between September 2015 and April 2016 families were contacted and asked to take part in the 10-year follow-up study. In two patients (two in DRIFT, zero in standard treatment), we were unable to find a contact address or number. This left 67 patients where the survival status was known. Of these, there were two deaths in the DRIFT arm and two deaths in the standard treatment arm, one patient declined (in the standard treatment arm) and 10 gave no response, leaving 52 available for assessment: 28 in the DRIFT arm and 24 in the standard treatment arm.

Among the 52 children available for follow-up assessments at 10 years, there were imbalances of gender and birthweight favouring the standard treatment group. There were 22 males in the DRIFT arm (79%) whereas the standard treatment arm had a lower proportion of males (63%). Birthweight was much higher in the standard treatment arm (mean 1322 g) than in the DRIFT arm (1102 g). We prespecified in the analysis plan that any baseline characteristics that differed by more than 10%/0.5 SDs would be adjusted for in a sensitivity analysis.

Cognitive disability

Given the larger than expected attrition rate, precision was lower than hoped and was exacerbated further by large SDs for the cognitive ability quotient. Despite this, results are in parallel with those at 2 years, with crude estimates giving weak evidence that the DRIFT intervention increases cognitive ability at 10 years ($p = 0.096$). After adjusting for the prespecified covariates of gender, birthweight and grade of IVH, this evidence was strengthened and indicated that children who were in the DRIFT arm of the trial, on average, had a CQ score of 23.5 points higher than those who received standard treatment ($p = 0.009$). This translates into a developmental cognitive advantage of 2.5 years.

Sensitivity analysis for primary outcome

The binary outcome, alive without severe cognitive disability, gave very similar results to the continuous CQ outcome [unadjusted OR 3.6, 95% confidence interval (CI) 1.2 to 11.0; $p = 0.026$ and adjusted OR 10.0, 95% CI 2.1 to 46.7; $p = 0.004$]. Both the unadjusted and adjusted model gave strong evidence to suggest that DRIFT had a positive impact on children's cognitive outcomes at 10 years. The number needed to treat was three.

Vision

Overall, the results show that those in the DRIFT arm were almost four times more likely to have a 'good' visual outcome than the standard treatment arm (adjusted OR 3.73); however, the p -value shows only very weak evidence to support this ($p = 0.136$). No difference was found in CVI mean score (-0.12 , 95% CI -0.47 to 0.24 ; $p = 0.502$).

Sensorimotor disability

There was no difference in mean Movement ABC scores (-1.0 , 95% CI -16.8 to 14.8 ; $p = 0.896$). Children in the DRIFT arm were 1.1 times more likely to have CP than those in the standard treatment arm (OR 1.10, 95% CI 0.36 to 3.35; $p = 0.862$). After adjustment for gender, birthweight and grade of IVH, this changed to 63% lower odds of CP in the DRIFT group (OR 0.37, 95% CI 0.07 to 2.00; $p = 0.249$); this is largely due to those in the DRIFT having less favourable baseline characteristics. Although the percentage of children with CP was higher in the DRIFT arm than in the standard treatment arm (61% vs. 58%, respectively), those in the DRIFT arm were less likely to have CP categorised as severe. After adjustment, those in the DRIFT arm were 32% more likely to be ambulant than those in the standard treatment arm (1.32, 95% CI 0.24 to 7.25; $p = 0.751$). However, given the large CI and p -value, the evidence to support this finding was not strong; the result could have simply happened by chance.

Emotional/behavioural function

There was no difference in mean SDQ score ($p = 0.584$).

Neuroimaging

There were no major differences relating to residual neurosurgical conditions needing referral. Residual catheter tracks were more often seen in the standard treatment group and in association with ventricular reservoirs.

Education outcomes

After adjustment, those in the DRIFT arm had lower odds (0.27) of special school attendance in the last 12 months than those in the standard treatment arm ($p = 0.059$).

Harms

Despite the excess secondary haemorrhages in the DRIFT group, the primary outcomes were better and the secondary outcomes were no worse than in the standard treatment group. It does not appear that secondary haemorrhages that occurred during the DRIFT procedure had a long-term detrimental effect. High-resolution structural brain MRI at 10 years showed no evidence of damage associated with insertion of the DRIFT irrigation catheters. There was no difference in ongoing neurosurgical problems between the treatment arms at age 10 years.

Cost of initial hospitalisation

Participants allocated to DRIFT had irrigation therapy for an average of 5.2 days at an estimated cost of £1513 per participant. Some of this initial cost of DRIFT was offset by the fact that fewer patients had reservoir procedures during the neonatal stay. The total mean costs of the neonatal stay were higher in patients who had DRIFT, but the CI was wide and included zero (unadjusted mean difference £6556, 95% CI –£11,161 to £24,273). The finding was sensitive to adjustment for covariates, particularly birthweight. After adjustment for birthweight, gender and IVH grade, estimated mean costs of neonatal care were lower in patients who had DRIFT although CIs were still wide and included zero (adjusted mean difference –£3056, 95% CI –£19,449 to £13,335).

Postnatal hospital admissions and total NHS secondary care costs

Participants allocated to DRIFT spent an average of 19.4 additional days in hospital up to age 2 years and an average of 26.6 additional days in hospital between age 2 years and 31 March 2016. Participants allocated to standard care spent fewer additional days in hospital (8.8 days at age 0–2 years; 18.5 days at age 2 years upwards). The unadjusted total costs of hospital care after the initial neonatal stay were higher in participants allocated to DRIFT (unadjusted mean difference £3413, 95% CI £12,408 to £19,234). This finding was very sensitive to adjustment for covariates, particularly gender and birthweight. After adjustment, the estimated mean cost among participants allocated to DRIFT was lower (adjusted mean difference –£9739, 95% CI –£27,558 to £8080).

Use of ambulatory health and social care at ten-year follow-up

There was little evidence of a difference in emergency and outpatient care in the last 12 months at 10-year follow-up. Participants in both arms of the trial reported an average of just over 0.4 visits to the emergency department and just over 2.8 outpatient clinic visits. The adjusted mean difference in costs was marginally higher in participants allocated to DRIFT (adjusted mean difference £2, 95% CI –£264 to £267). The costs of other ambulatory care during the last 6 months were higher in participants randomised to standard care (adjusted mean difference –£108, 95% CI –£596 to £380) but the CI was wide.

Family income, expenses and child's educational needs

Overall, a similar proportion of parents/carers were employed at the 10-year follow-up. However, a lower proportion of households of participants who received DRIFT had benefits as their main source of income (adjusted OR 0.23, 95% CI 0.04 to 1.22), although the CI included 1. A higher percentage of parents of participants in the standard treatment arm reported that their child attended a special unit or special school (adjusted OR 0.13, 95% CI 0.02 to 0.82). Owing to the high cost of special schooling, this is potentially economically important; the adjusted mean difference in estimated annual school costs was –£5321, 95% CI –£9772 to –£870.

Health-related quality of life

In adjusted analyses, both the EQ-5D-5L and HUI3 scores of HRQoL tended to be higher in survivors who were allocated to DRIFT than in those who were allocated to standard care. However, the CIs around the adjusted mean differences in EQ-5D-5L score (0.06, 95% CI –0.11 to 0.22) and HUI3 score (0.13, 95% CI –0.09 to 0.35) included zero.

Decision analytical model

DRIFT has the potential to be a cost-effective intervention at current NICE thresholds. Exploratory analysis using a simulation model to interpolate and extrapolate costs and outcomes to age 18 years indicated that the additional benefit [8.96 quality-adjusted life-years (QALYs) vs. 8.33 QALYs] in the DRIFT arm justifies the higher NHS and social service costs (£112,341 vs. £102,611). The incremental cost-effectiveness ratio (£15,621) was below the NICE thresholds of £20,000 to £30,000 per QALY and the incremental net monetary benefit (£2711) was positive. When education costs are included or using costs and utility scores adjusting for gender, IVH grade and birthweight, DRIFT has the potential to both save money and improve outcomes for children.

Conclusions

Implications for health care

The school-age follow-up of the DRIFT trial strengthens the evidence of benefit found at 2 years and adds further evidence of safety of the intervention. We can conclude that DRIFT improves cognitive function when taking into account birthweight, IVH grade and gender. The cost of the intervention is moderate; DRIFT has the potential to be cost-effective. In some scenarios, DRIFT may save money and improve outcomes owing to the possible reduction in the need for special education.

Recommendations for research

The role of any NHS implementation of DRIFT, ideally in a few specialised tertiary centres, delivered through the existing neonatal operational delivery networks, will need to be studied prospectively in a multicentre trial. As well as measures of cognition and functional measures, the data from the 10-year outcomes indicate that any future studies should continue to collect data on vision, motor skills and education, given the trends seen in the secondary outcomes that the study was not powered to address.

A larger proportion of infants with PHVD is now extremely immature. Further refinements in DRIFT may need to be studied in this very immature group of patients.

For infants with parenchymal infarction in addition to PHVD, there is scope to supplement DRIFT with novel interventions to promote brain tissue repair in the future.

Trial registration

This trial is registered as ISRCTN80286058.

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