Silver-impregnated, antibiotic-impregnated or non-impregnated ventriculoperitoneal shunts to prevent shunt infection: the BASICS three-arm RCT

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Scientific summary

The BASICS three-arm RCT

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Scientific summary

Background

Hydrocephalus affects one in every 500 births; thus, it is one of the most common developmental disabilities in children. The condition also affects older children and adults of all ages, and can be secondary to a variety of causes, including intracranial tumours, haemorrhage and infection.

Standard treatment for hydrocephalus remains the ventriculoperitoneal shunt. Insertion of a ventriculoperitoneal shunt to treat hydrocephalus is now one of the most common procedures performed in neurosurgical units, and between 3000 and 3500 shunt operations are carried out per year in the UK in adults and children. Currently, three types of shunt catheter are available: standard silicone shunts (hereafter referred to as standard shunts), antibiotic-impregnated shunts (hereafter referred to as antibiotic shunts) and silver-impregnated shunts (hereafter referred to as silver shunts). There is no standard practice or guidance in the UK as to which shunt catheter is the most effective at reducing infection.

The incidence of shunt infection varies markedly in the literature from 3% to 27%, and is higher in certain groups, such as neonates and children aged < 1 year. Episodes of shunt infection have a significant impact on patients and the NHS and require prolonged inpatient hospitalisation, additional surgery to remove the infected hardware, intravenous and intrathecal antibiotics, and further surgery to place a new shunt once the infection has been treated. This trial, therefore, addresses the primary question of which shunt catheter is the most effective in reducing shunt infection and has secondary questions addressing the consequences of infection in a clinical and financial context.

Objectives

The trial addressed the following objectives.

Primary outcome

The primary outcome was the time to failure of a first ventriculoperitoneal shunt due to infection, as assessed by a blinded central review panel. The central review panel comprised the chief investigator (or delegate, for participants treated by the chief investigator) and a microbiologist, both of whom were masked to participant allocations.

Secondary outcomes

The secondary outcomes were to compare the following outcomes in the standard shunt arm with the antibiotic and silver shunt arms, respectively:

- time to removal of a first ventriculoperitoneal shunt due to suspected infection, as assessed by the treating surgeon
- time to ventriculoperitoneal shunt failure for any cause
- reason for failure (infection, mechanical, patient, functional)
- types of bacterial ventriculoperitoneal shunt infection (organism, antibiotic resistance)
- time to ventriculoperitoneal shunt infection following first clean (non-infected) revision
- quality of life, assessed using the Hydrocephalus Outcome Questionnaire
- incremental cost per ventriculoperitoneal shunt failure (any cause) averted
- incremental cost per quality-adjusted life-year gained.

Methods

Participants

Participants were screened for eligibility in 21 neurosurgical units across the UK and the Republic of Ireland. All participating centres met the British Antibiotic and Silver Impregnated Catheters for ventriculoperitoneal Shunts (BASICS) centre inclusion criteria.

Patients were eligible to participate in the trial if they had hydrocephalus of any aetiology (including idiopathic intracranial hypertension) requiring a first ventriculoperitoneal shunt. Note that failed primary endoscopic third ventriculostomy, indwelling ventricular access device (e.g. Ommaya or Rickham reservoir or ventriculosubgaleal shunt or similar) and indwelling external ventricular drains were allowed.

Patients with the following characteristics were excluded from the trial:

- previous indwelling ventricular or lumbar peritoneal or atrial shunt
- active and ongoing cerebrospinal fluid or peritoneal infection (previous infected cases were allowed once cleared of infection)
- multiloculated hydrocephalus requiring multiple ventriculoperitoneal shunts or neuroendoscopy
- ventriculoatrial or ventriculopleural shunt planned
- allergy to antibiotics associated with the antibiotic shunt
- allergy to silver.

Trial procedures

Patients were eligible to be randomised to the trial if written consent was provided by the patient, parent, legal representative or consultee, as appropriate. Patients were randomised, by envelope, in a ratio of 1 : 1 : 1 in the operating theatre at the time when the ventriculoperitoneal shunt was required. The randomisation sequence was generated by an independent statistician and stratified by neurosurgical unit, age group (adult or paediatrics were defined according to unit practice) and envelope storage room within the neurosurgical unit. Patients and a central review panel, but not surgeons or operating staff, were blinded to the type of ventriculoperitoneal shunt inserted. All ventriculoperitoneal shunt types were medical devices used in accordance with the manufacturers' instructions for their intended purpose.

All patients having a first ventriculoperitoneal shunt for hydrocephalus of any aetiology (including idiopathic intracranial hypertension) were screened for eligibility and recorded on a centre-held screening log. Reasons for non-recruitment were documented (e.g. not eligible, declined consent) and the information was used for monitoring purposes.

Data were collected at baseline (pre-operative assessment), randomisation (first surgery), early post-operative assessment, first routine post-operative assessment, 12-weekly follow-up assessments, subsequent routine post-operative assessments and, when applicable, unscheduled visits/admissions and at shunt revision/removals. Patients were followed for a minimum of 6 months and a maximum of 2 years.

An economic evaluation was conducted to estimate the incremental cost-effectiveness of impregnated ventriculoperitoneal shunt catheters, expressed as all-cause ventriculoperitoneal shunt failures averted.

Sample size

The sample size for the primary outcome was calculated using the Pintilie method (Pintilie M. Dealing with competing risks: testing covariates and calculating sample size. *Stat Med* 2002;**21**:3317–24), and assumed the following: (1) failure due to infection was the event of interest, with all other reasons for failure a competing risk; (2) the rate of infection was 8% in the standard silicone arm and 4% in the impregnated shunt catheter arms; (3) the competing risk event rate was 30%; and (4) a 5% loss to

follow-up. An initial total sample size of 1200 with 119 events demonstrated good statistical power (88%), with leverage for a lower event rate if required.

Ongoing monitoring of the infection rate identified a deviation from the assumptions and, subsequently, a need to revise the original sample size. In January 2016, the target sample size was increased to 1606 participants with 101 events and 80% power. The Independent Data and Safety Monitoring Committee oversaw this revision and the Trial Steering Committee agreed and approved this change.

Statistical analysis

Efficacy outcomes were analysed according to the intention-to-treat principle, as far as practically possible, and safety analyses were analysed according to the type of ventriculoperitoneal shunt in situ. A Bonferroni adjustment was made to allow for multiple comparisons and a 2.5% statistical significance level, and 97.5% confidence intervals were used throughout. The statistical analysis plan was developed prior to analysis.

Outcomes with infection as the event of interest used Fine and Gray (Fine PF, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc* 1999;**94**:496–509) survival regression models with cause-specific hazard ratios and subdistribution hazard ratios presented. Cox regression models were used to analyse time to ventriculoperitoneal shunt failure as a result of any cause. Reason for ventriculoperitoneal shunt failure is presented descriptively and with a chi-squared test. Types of organisms, and their resistances and sensitives, are presented descriptively. Quality-of-life outcomes were analysed using mixed models.

Economic evaluation

The health economic analysis adopted the perspective of the NHS and Personal Social Services. Costs (2016/17) were estimated from questionnaires, entries made in case report forms and from patient-level information and costing systems. The primary economic effectiveness outcome was ventriculoperitoneal shunt failure as a result of any cause, with failure due to infection and quality-adjusted-life years – based on responses to the EuroQol-5 Dimensions, three-level version – as important secondary outcomes. Costs and benefits occurring after the first year were discounted at 3.5% per annum. The joint uncertainty in costs and benefits were considered in regression analyses and in non-parametric bootstrapping. Stratified cost-effectiveness analyses considered important subgroups [paediatrics (aged up to 16 years), adults aged 16–65 years and adults aged > 65 years].

Results

Participants

A total of 3505 patients were screened for eligibility from 21 centres, 1605 of whom were subsequently randomised. The overall consent rate in patients who were approached for consent was 82% ($n = 1672/2041$). The three arms were similar in their baseline characteristics and their baseline risk assessments. Approximately 40% of all participants were admitted as paediatric patients ($n = 599/1605$) and one-quarter of all participants were aged < 1 year.

The randomised groups were approximately equal in size (standard shunt: $n = 536$; antibiotic shunt: $n = 538$; silver shunt: $n = 531$). Of those randomised, 1585 (98.8%, $n = 1605$) received the ventriculoperitoneal shunt as randomised; 16 (1.0%) received an alternative trial ventriculoperitoneal shunt; and four (0.2%) received no ventriculoperitoneal shunt.

Primary outcome: time to failure of first ventriculoperitoneal shunt due to infection, as assessed by a blinded central review panel

Seven patients had an infection at insertion and were not included in the primary outcome set. Of those remaining ($n = 1594$), 398 patients had revision operations (25.0%), with 75 being centrally classified as having ventriculoperitoneal shunt infections (4.7%). The rate of infection was approximately equal in the standard and silver shunt arms [6.0% ($n = 32/533$) and 5.9% ($n = 31/526$), respectively] and lower in the antibiotic shunt arm (2.2%, $n = 12/535$).

When compared with the standard shunt, antibiotic shunts decreased the risk of infection (cause-specific hazard ratio 0.38, 97.5% confidence interval 0.18 to 0.80). Silver shunts were comparable to standard shunts (cause-specific hazard ratio 0.99, 97.5% confidence interval 0.56 to 1.74). The majority of centrally assessed infections were classified as definite – culture positive ($n = 53/75$, 70.7%).

Secondary outcome 1: time to removal of first ventriculoperitoneal shunt due to suspected infection, as assessed by the treating surgeon

Of the 398 revisions, 78 (4.9%) were defined by the treating surgeon as being due to suspected infection. As with the primary outcome, when compared with the standard shunt, the antibiotic shunt, but not the silver shunt, was associated with a significant decrease of infection [antibiotic shunt: cause-specific hazard ratio 0.45 (97.5% confidence interval 0.23 to 0.91), silver shunt: cause-specific hazard ratio 0.93 (97.5% confidence interval 0.53 to 1.64)].

Secondary outcome 2: time to ventriculoperitoneal shunt failure due to any cause

The revision rate was approximately equal across the three arms, and varied from 24.4% in the standard shunt arm ($n = 103/533$) to 25.9% in the silver shunt arm ($n = 136/526$). No significant difference was observed for time to failure between the antibiotic and silver shunt arms when compared with the standard shunt [antibiotic shunt: hazard ratio 1.01 (97.5% confidence interval 0.77 to 1.33), silver shunt: hazard ratio 1.08 (97.5% confidence interval 0.82 to 1.42)].

Secondary outcome 3: reason for shunt failure

Although the number of ventriculoperitoneal shunt failures was similar between the three arms, the underlying reason, as classified by the treating surgeon, differed when comparing the standard shunt with the antibiotic shunt ($p = 0.02$); there were fewer infections with antibiotic shunts, but a higher frequency of failure due to other causes. The underlying reason did not differ significantly when comparing the standard shunt with the silver shunt ($p = 0.71$).

Secondary outcome 4: type of bacterial infection

The central review panel classified all shunt infections that were 'definite – culture positive' and 'probable – culture uncertain' ($n = 56/75$) by one organism that was cultured. *Staphylococcus aureus* accounted for 30% of cultured organisms in ventriculoperitoneal shunt infection ($n = 17/56$).

Secondary outcome 5: time to ventriculoperitoneal shunt infection following first clean revision

Among participants with a first clean (non-infected) revision ($n = 323$), the proportion with a subsequent revision for any reason was 39.6% ($n = 128/323$). This rate was 25% ($n = 398/1594$) in participants with de novo ventriculoperitoneal shunts. The infection rate was 6.2% ($n = 20/323$) for participants who had their de novo shunt revised for reasons other than infection ($n = 323$) and subsequently went on to have this replacement shunt revised due to infection ($n = 20$). This infection rate was higher than that for de novo ventriculoperitoneal shunts [4.7% ($n = 75/1594$)]. However, there was no significant between-group difference in time to infection following first clean revision when comparing either antibiotic or silver shunts with the standard shunt [antibiotic shunt: cause-specific hazard ratio 0.55 (97.5% confidence interval 0.17 to 1.75); silver shunt: cause-specific hazard ratio 0.48 (97.5% confidence interval 0.14 to 1.67)].

Secondary outcome 6: quality of life, assessed using Hydrocephalus Outcome Questionnaire

Insufficient data were returned to formally analyse the Hydrocephalus Outcome Questionnaire results.

Cost-effectiveness analysis

Secondary outcome 7: incremental cost per ventriculoperitoneal shunt failure averted

In the base-case analysis, both antibiotic and silver shunts were located in the south-west quadrant of the cost-effectiveness plane, in relation to the standard shunt. Incrementally, silver shunts save £62,358 for each additional failure compared with standard shunts, and antibiotic shunt catheters save £638,600 per additional failure compared with silver shunts.

Secondary outcome 8: incremental cost per quality-adjusted life-year gained

Based on the incremental cost per confirmed ventriculoperitoneal shunt infection averted, antibiotic shunt catheters were dominant, saving £4059 (97.5% confidence interval −£1422 to £12,567) per 0.030 (97.5% confidence interval 0.002 to 0.058) fewer infection-related ventriculoperitoneal shunt failures; compared with the standard shunt, antibiotic shunt catheters save £135,753 per ventriculoperitoneal shunt infection avoided. Silver shunt catheters were dominated by the standard shunt.

In the cost–utility analysis of trial participants aged ≥ 5 years, antibiotic shunt catheters were dominated by silver shunts. Compared with standard shunts, the incremental cost-effectiveness of silver shunts was £1904 per quality-adjusted life-year gained. The probabilities of cost-effectiveness at £20,000 per quality-adjusted life-year are 0.206 (standard shunt), 0.274 (antibiotic shunt) and 0.52 (silver shunt); at £30,000 per quality-adjusted life-year, the cost-effectiveness probabilities are 0.147 (standard shunt), 0.267 (antibiotic shunt) and 0.586 (silver shunt).

Adverse events

There were no serious adverse events. A total of 654 adverse events were reported in 413 patients (constituting 25.8% of $n = 1601$ participants who received a de novo shunt). The proportion of patients experiencing an event was similar across the arms (standard shunt: $n = 135/531$, 25.4%; antibiotic shunt: $n = 136/545$, 25.0%; silver shunt: $n = 140/525$, 26.7%). Common adverse events were ventricular shunt catheter obstruction (96 events in 79/1601 patients, 4.9%), shunt valve obstruction (65 events in 52/1601 patients, 3.2%) and valve change for symptomatic over-/underdrainage (54 events in 50/1601 patients, 3.1%).

Conclusions

Implications for health care

Antibiotic ventriculoperitoneal shunt reduces the infection rate compared with standard shunts, and, in doing so, is cost-saving. Silver ventriculoperitoneal shunts are not associated with a lower rate of infection. The significant effective benefit for the patient of the antibiotic shunt in reducing shunt infection, combined with the economic benefit in terms of costs saved per ventriculoperitoneal shunt infection averted, would support all patients receiving an antibiotic-impregnated ventriculoperitoneal shunt at first shunt insertion.

Implications for research

The BASICS trial is the largest prospective randomised trial on ventriculoperitoneal shunts for hydrocephalus ever performed, to our knowledge. The information collected will fuel many future studies on both the molecular biology of infection and the reasons behind both infective and mechanical shunt failure.

Trial registration

This trial is registered as ISRCTN49474281.

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This report

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