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ORIGINAL PAPER

International Infant Hydrocephalus Study (IIHS): 5-year health outcome results of a prospective, multicenter comparison of endoscopic third ventriculostomy (ETV) and shunt for infant hydrocephalus

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Abstract

Introduction One of the most important unanswered questions in pediatric hydrocephalus is determining whether treatment with endoscopic third ventriculostomy (ETV) versus shunt results in improved health status and quality of life (QOL). To answer this, the International Infant Hydrocephalus Study (IIHS) was started in 2005 as a prospective, multicenter study to compare ETV and shunt in infants (< 24 months old) with symptomatic triventricular hydrocephalus from aqueductal stenosis. Herein, we present the 5-year primary outcome results.

Methods IIHS utilized a prospective comprehensive cohort design, in which patients received ETV or shunt, based on either randomization or parental preference. For this analysis, we pooled the randomized arm and the parental preference arm, analyzing them together. At 5 years of age, children were assessed with the Health Utilities Index Mark 2 (HUI-2) (primary outcome) and the Hydrocephalus Outcome Questionnaire (HOQ), a measure of QOL. Results were compared in an analysis of covariance, adjusting for baseline variables including age at surgery and baseline development status.

Results From a total of 158 patients who met eligibility criteria, complete 5-year outcomes were available on 78 (19 treated initially with shunt, 61 treated initially with ETV), assessed at a mean age of 62.1 months (SD 6.3). The mean 5-year HUI-2 utility score was 0.90 (SD 0.19) for ETV and 0.94 (SD 0.10) for shunt ($p = 0.21$). The mean 5-year HOQ overall score was 0.81 (SD 0.15) for ETV and 0.85 (SD 0.12) for shunt ($p = 0.42$). Similarly, there were no significant differences noted between 5-year HOQ subscores (cognitive, social-emotional, physical) or developmental measures at 1, 2, and 3 years.

Conclusions This is the first prospective direct comparison of long-term outcomes of ETV and shunt for infant hydrocephalus. These results suggest that overall health status and quality of life in this cohort of infants treated for aqueductal stenosis are high, with no significant difference between those treated initially with ETV or shunt.

Trial registration NCT00652470

Keywords International Infant Hydrocephalus Study · Endoscopic third ventriculostomy · Shunt · Hydrocephalus

Introduction

One of the principle unanswered issues in pediatric hydrocephalus is the impact on quality of life (QOL) and health status of endoscopic third ventriculostomy (ETV) versus CSF shunt. The current literature is quite limited, with virtually no long-term comparative prospective studies available. The International Infant Hydrocephalus Study (IIHS) was an international, prospective, multicenter study that aimed to answer the question: in infants (< 24 months old) with symptomatic triventricular hydrocephalus from aqueductal stenosis, does initial treatment with ETV result in superior or no worse outcome at 5 years of age compared

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to shunt? The study began enrollment in 2005 across four continents, and we have previously presented preliminary results from the IIHS cohort regarding treatment failure [1, 2]. Here, we present our analysis of the 5-year primary outcome results for health status and QOL.

Methods

The IIHS was a prospective study that initially included both randomized and non-randomized arms [1, 3], but because of poor recruitment into the randomized arm, all subsequent analyses have combined the groups into a prospective non-randomized comparison of ETV and shunt [1, 2]. All involved centers were experienced in infant neuroendoscopy (≥ 10 neuroendoscopic procedures per year per surgeon and ≥ 2 ETV operations in infants per surgeon in total). The patient eligibility criteria were as follows: < 24 months of age at time of operation, symptomatic triventricular hydrocephalus (TVH) requiring first treatment, born at > 36 weeks gestation, preoperative MRI showing aqueductal stenosis with no other major brain anomalies. Patients with a history of intraventricular hemorrhage (intra-uterine or post-natal) or intracranial infection were included, unless this related to prematurity. Patients were excluded if they had the following: open spina bifida, Dandy-Walker syndrome with vermian agenesis/dysgenesis, perinatal asphyxia, severe brain dysmorphic anatomical features, known chromosomal abnormality, or intracranial tumor. Eligibility criteria were independently adjudicated for all patients.

Intervention Patients were allocated to intervention by either 1:1 randomization or family preference. The ETV intervention consisted of a standard frontal burr hole and use of an endoscopic camera to visualize the floor of the third ventricle. A ventriculostomy was created using the surgeon's own preferred method of perforation. At the surgeon's discretion, a post-operative temporary external ventricular drain or reservoir was inserted. The ventriculoperitoneal shunt intervention involved creating a burr hole in the frontal or occipital regions and cannulating the ventricle with a silastic catheter. This was then attached to a valve mechanism of the surgeon's choice and distal silastic tubing which ran subcutaneously to the peritoneal cavity. Prophylactic antibiotics were used.

Follow-up At enrollment, baseline clinical data were collected. Following the initial intervention (ETV or shunt), patients were regularly followed as per departmental and surgeon routine, but with scheduled visits at 1, 2, 3, and 5 years after surgery. All data were collected prospectively. Aside from standard clinical outcome metrics, the following were also assessed:

Ventricle size: Follow-up MR imaging taken at 3 years was used to determine ventricle size by measuring the frontal-occipital horn ratio (FOR) [4, 5].

Denver II Developmental Screening Test (DDST): The DDST is a widely used screening tool designed to identify developmental delay in infants and children [6]. It provides a list of age-specific tasks and milestones in the domains of social, fine motor, language, and gross motor. The evaluator determines if the infant can perform each of these age-specific tasks and milestones. For analysis, we derived a DDST score, which was calculated by dividing the total number of tasks achieved by the number of tasks expected for age across all domains, multiplied by 100. The DDST score, therefore, ranged from 0 to 100, with higher scores indicating better developmental status. The DDST was performed at pre-operative baseline and at 1, 2, and 3-year follow-up.

Hydrocephalus Outcome Questionnaire (HOQ): The child's primary caregiver completed the HOQ, a 51-item questionnaire with proven reliability and validity in measuring health outcome and quality of life in children with hydrocephalus [7–10]. The HOQ provides scores of overall health, physical health, cognitive health, and social-emotional health, all of which range from 0 (worse outcome) to 1.0 (better outcome). Previous work has suggested that a clinically meaningful difference in HOQ score is approximately 0.10 [11]. The HOQ was administered at 5-year follow-up.

Health Utilities Index Mark 2(HUI-2): Caregivers also completed the HUI-2 which provided information about the functional health status of the child in the domains of sensation, mobility, emotion, cognition, self-care, and pain. From these, an overall HUI-2 utility score, ranging from 0 to 1.0 with higher scores indicating better status, was calculated [12–14]. The HUI-2 was administered at 5-year follow-up and was the primary outcome of IIHS.

Sample size The initial expected sample size was 182 randomized patients and was powered to detect a 0.10 difference in 5-year health status using the HUI-2 utility score [10]. Study recruitment began in 2005, but because enrollment in the randomized arm was slower than anticipated, recruitment was stopped in December 2013 at the recommendation of the Data Safety Monitoring Committee (DSMC) on the basis of futility of reaching the targeted randomized cohort sample size.

Analysis For these analyses, and as per the suggestion of the DSMC, the randomized and non-randomized arms were pooled to compare those who underwent ETV versus shunt as their first surgical intervention. Baseline data between these two groups were compared to determine

imbalances in pre-operative characteristics, using *t* test or Fisher's exact test, as appropriate.

The primary analysis of this paper was an analysis of covariance (ANCOVA) comparing the 5-year HUI-2 utility score between ETV and shunt, adjusting for patient age at first surgery (months), baseline DDST score, history of infection/hemorrhage (yes/no), geographical continent (since there were too few patients to adjust by individual center or country), and randomization status (i.e., whether the patient entered the study in the randomized or non-randomized arm). Geographical continent was categorized as the Americas (since there only a few patients from North America alone), Europe, and Asia.

For secondary analyses, the ANCOVA was repeated using the following as the dependent variables: HOQ overall score, HOQ cognitive score, HOQ social-emotional score, HOQ physical score, 12-month DDST score, 24-month DDST score, and 36-month DDST score.

As a post hoc analysis, we aimed to determine the effect of ventricle size on 5-year outcome. To do this, the ANCOVA models for 5-year outcomes were re-tested with the addition of 3-year ventricle size as an independent variable.

Descriptive data are presented as mean (standard deviation) or number (percent).

The IIHS was publically registered (clinicaltrials.gov, NCT00652470) and received ethics approval from all participating institutions. Participating investigators and other trial personnel are listed in the "Acknowledgements."

Results

Of 158 eligible patients, full 5-year primary outcome data and follow-up was available on 78 (39 from Europe, 27 from Asia, and 12 from the Americas). Figure 1 shows the flow of patients in the study. Baseline data for these 78 patients are shown in Table 1. There were no significant differences in baseline characteristics, although the ETV group was slightly older and with slightly larger ventricle size.

Failure of first treatment occurred in 21 (35.6%) of the ETV patients and 4 (21.1%) of the shunt patients ($p = 0.27$). Our more detailed analyses of treatment failure are available elsewhere [1, 2].

The mean (SD) age in months at the 1-, 2-, 3-, and 5-year assessments was 13.6 (4.1), 25.0 (3.7), 37.0 (5.1), and 62.1 (6.3).

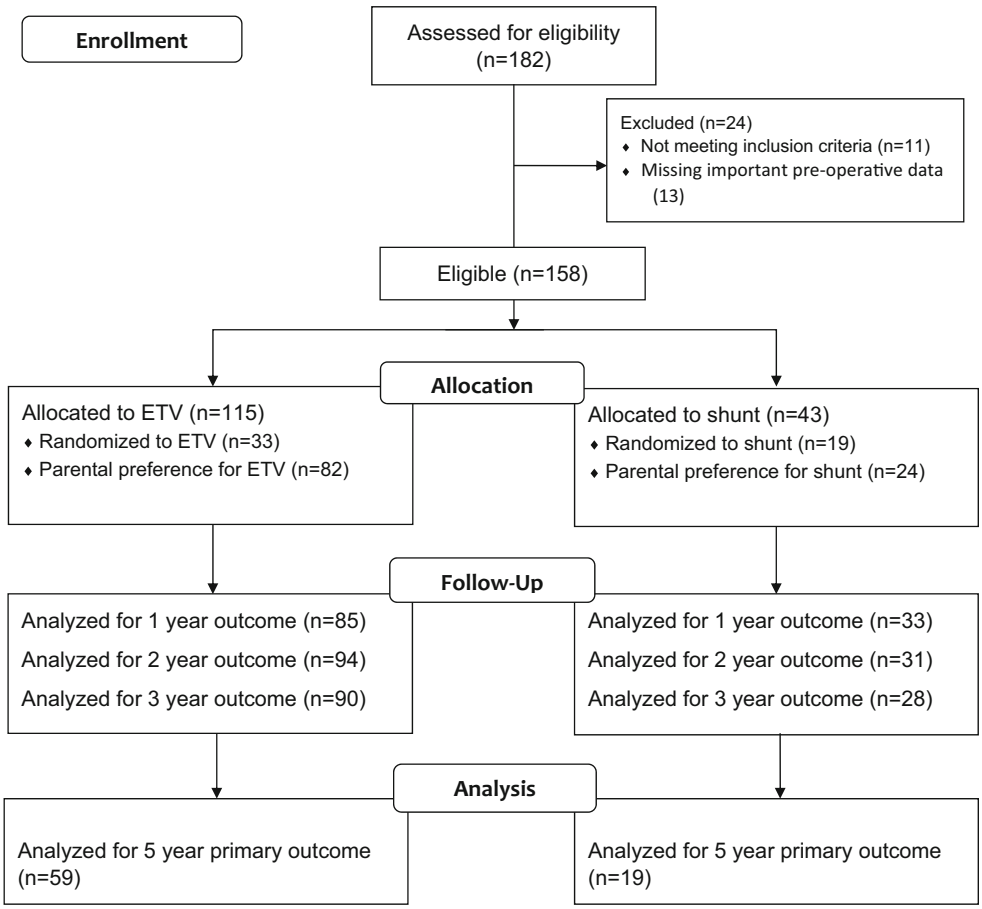

Fig. 1 Patient enrollment and flow

Table 1 Patient characteristics at baseline

	Overall ($N = 78$)	ETV ($n = 59$)	Shunt ($n = 19$)	p value
Age in months at first surgery (mean, SD)	5.1 (5.4)	5.6 (5.2)	3.8 (5.6)	0.21
Female sex (number, %)	34 (43.6%)	25 (42.4%)	9 (47.4%)	0.79
History of infection (number, %)	5 (6.4%)	3 (5.1%)	2 (10.5%)	0.59
History of hemorrhage (number, %)	4 (5.1%)	3 (5.1%)	1 (5.3%)	1.0
Length of initial hospitalization, days (median, IQR)	7.9 (6.6)	7.7 (5.8)	8.5 (8.8)	0.64
DDST score (mean, SD)	63.0 (22.4)	62.4 (23.6)	64.9 (18.9)	0.67
Ventricle size, frontal-occipital horn ratio (mean, SD)	0.59 (0.08)	0.60 (0.08)	0.56 (0.10)	0.07

Results for the primary outcome are shown in Table 2. There was no significant difference in the 5-year HUI-2 utility score between ETV and shunt (adjusted p value 0.21). Similarly, there was no significant difference in any of the HOQ scores at 5 years. Results of the 1-, 2-, and 3-year outcomes are shown in Table 3. These also showed no significant difference between treatments in DDST score.

At 3 years, ventricle size in the ETV group (0.43 [0.11]) was slightly larger than the shunt group (0.38 [0.07]), but this was not statistically significant ($p = 0.10$). With the addition of 3-year ventricle size into the ANCOVA models, the results were similar, showing no significant differences between ETV and shunt for any 5-year outcome (adjusted p values ranged from 0.23 to 0.84). As well, in these models, ventricle size was also not significantly associated with any outcome (adjusted p values ranged from 0.30 to 0.83).

Discussion

The impact of ETV compared to shunt on long-term outcome is not known and has been one of the most important questions in pediatric hydrocephalus. Previous attempts to compare QOL and developmental outcome between these treatments have often been limited by retrospective design and relatively heterogeneous patient populations. For example, Kulkarni et al. used cross-sectional data in a large, diverse population of children with hydrocephalus [15]. In another study, the same group compared QOL in a smaller, more restricted group of older children with discreet obstructive hydrocephalus and, in a subset, also compared neurocognitive outcome [16]. Despite the limitations of those studies, neither was able to show a significant difference in long-term QOL outcome between ETV and shunt.

We believe that our prospective, multicenter study of ETV versus shunt for triventricular hydrocephalus in infants provides the best available data to date comparing these two procedures. Our study failed to show a meaningful difference in 5-year QOL and health status outcome between the two procedures. Virtually, all differences in 5-year outcome were not significant and the magnitude of the differences was estimated to be quite small. The one exception to this was HOQ cognitive score, for which the estimate of difference between ETV and shunt bordered on meaningful in favor of shunt, but remained statistically non-significant. We do not know if this simply reflects a limitation of our sample size, and perhaps, with a larger sample, a significant difference in HOQ cognitive might have been revealed. This is notable because one of the concerns with ETV is that it does not reduce ventricle size as reliably as shunt. This was evident in our cohort, although the difference in ventricle size was not statistically significant.

Table 2 Five-year outcome results

	Overall	ETV	Shunt	Adjusted difference between ETV and shunt (95% confidence interval)*	Adjusted p value*
HUI-2 utility score (mean, SD)	0.91 (0.18)	0.90 (0.19)	0.94 (0.10)	− 0.06 (− 0.14 to 0.03)	0.21
HOQ overall score (mean, SD)	0.82 (0.15)	0.81 (0.15)	0.85 (0.12)	− 0.03 (− 0.11 to 0.05)	0.42
HOQ cognitive score (mean, SD)	0.76 (0.22)	0.74 (0.23)	0.84 (0.18)	− 0.10 (− 0.22 to 0.03)	0.12
HOQ social-emotional score (mean, SD)	0.84 (0.12)	0.83 (0.12)	0.87 (0.09)	− 0.04 (− 0.11 to 0.02)	0.18
HOQ physical score (mean, SD)	0.84 (0.19)	0.84 (0.20)	0.83 (0.17)	0.03 (− 0.07 to 0.12)	0.61

*Adjusted p values and adjusted differences were derived from ANCOVA models, adjusted for patient age at surgery, baseline DDST score, history of infection/hemorrhage, geographical continent, and randomization status

Table 3 Developmental outcome at 1, 2, and 3 years

	Overall	ETV	Shunt	Adjusted difference between ETV and shunt (95% confidence interval)*	Adjusted *p* value*
DDST scores at 1 year (mean, SD)	65 (22)	66 (22)	62 (26)	6 (3 to 14)	0.19
DDST scores at 2 years (mean, SD)	67 (24)	67 (25)	67 (20)	2 (7 to 11)	0.71
DDST Scores at 3 years (mean, SD)	70 (24)	70 (25)	71 (19)	1 (− 8 to 11)	0.78

*Adjusted *p* values and adjusted differences were derived from ANCOVA models, adjusted for patient age at surgery, baseline DDST score, history of infection/hemorrhage, geographical continent, and randomization status

Regardless, the impact of ventricle size on neurocognitive outcome is not clear [17, 19–25]. For example, a study of 23 children with long-standing stable hydrocephalus showed no correlation between ventricle size and neurocognitive outcome [17]. Others have suggested that, rather than ventricle size, it is actually brain volume that correlates best with neurocognitive outcome [18]. We did not find that ventricle size, as measured by FOR, impacted the statistically non-significant effects of treatment choice and nor was ventricle size independently associated with any 5-year outcome. One limitation of this analysis, however, is that we measured ventricle size at only 3 years, since 5-year ventricle size data was not available for most of the cohort. It would be expected, however, that the vast majority of children would have reached a stable ventricle size by 3 years that would carry over to 5 years. Furthermore, we also did not measure brain volume and future work will need to focus on this aspect.

It should be noted that the overall 5-year outcome in our cohort was excellent, with mean HOQ overall score of 0.82 and mean HUI-2 utility score of 0.91. These compare very favorably to a typical pediatric hydrocephalus population, in which equivalent scores are roughly in the 0.68 range for HOQ and 0.77 range for HUI-2 [7, 10, 19]. This is not entirely surprising, since our cohort consisted entirely of children with pure aqueductal stenosis and the absence of any other major neurological abnormalities. In fact, the overall HUI-2 utility score of 0.91 also compares well to the general population mean HUI-2 score of 0.95 for 8-year-old Canadian children (available from www.healthutilities.com, last accessed March 23, 2018). These data suggest that, regardless of treatment choice, the overall long-term prognosis for such infants is very good and this information can help counsel families.

The current study is novel in several ways. First, it is a truly prospective study designed with the 5-year outcome as the a priori primary goal [3]. To our knowledge, this is unique. Second, the patient population was well-defined and relatively homogeneous, consisting only of those with discreet aqueductal stenosis and triventricular hydrocephalus. This helps to remove at least some of the confounding in comparing outcome. Third, eligibility criteria were independently adjudicated ensuring that the patients truly represented the population of interest. Fourth, we used reliable and valid measures of outcome with the HUI-2 and the HOQ. Both of these measures have been widely used in describing outcome in pediatric hydrocephalus [8, 10, 19–21] and, therefore, are familiar to most neurosurgeons.

There are several limitations to our study. First, we were unable to successfully recruit enough patients into the randomized arm. In the absence of true randomization, the possibility of unaccounted confounding in our results remains. We tried to adjust for this using ANCOVA models, but this does not guarantee protection against confounding. Second, the assessment of outcome was not blinded, which could potentially bias results. However, the main outcome measures were largely parent-completed questionnaires, so the potential impact of surgeon bias on these should be minimal to nil. Third, despite being the largest study of its type, the overall sample size was still relatively small and lower than we had powered the study for. Therefore, it is possible that true differences in outcome might be missed by this study. As well, the analyzed sample of 78 patients represents only 49% of the 158 eligible patients who were enrolled in the study; this could be a biased representation of the overall cohort. Fourth, our study was limited to infants with aqueductal stenosis, so these results cannot necessarily be extrapolated to other etiologies of hydrocephalus or to children of a different age. As noted above, this is a particularly high-functioning group with overall good outcome, so it is not clear how applicable our results would be to those with an overall poorer long-term prognosis. Finally, our results speak only to initial treatment choice and do not shed light on how best to manage patients over the course of their childhood. That is, it must be recognized that we compared only ETV and shunt as the choice of first surgical intervention; many children went on to have subsequent surgeries, with some crossing over from ETV to shunt and vice versa. These choices were left entirely to the treating surgeon and were not accounted for in our analyses.

Conclusions

This is the first prospective direct comparison of long-term outcomes of ETV and shunt for infant hydrocephalus. These results suggest that overall health status and quality of life in this cohort of infants treated for aqueductal stenosis are high, with no significant difference between those treated initially with ETV or shunt.

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Compliance with ethical standards

The IIHS was publically registered (clinicaltrials.gov, NCT00652470) and received ethics approval from all participating institutions.

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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