Endoscopic third ventriculostomy and choroid plexus cauterization in infant hydrocephalus: a prospective study by the Hydrocephalus Clinical Research Network

Abhaya V. Kulkarni, MD, PhD,¹ Jay Riva-Cambrin, MD, MSc,² Curtis J. Rozzelle, MD,³ Robert P. Naftel, MD,⁴ Jessica S. Alvey, MSc,⁵ Ron W. Reeder, PhD,⁵ Richard Holubkov, PhD,⁵ Samuel R. Browd, MD, PhD,⁶ D. Douglas Cochrane, MD,¹ David D. Limbrick Jr., MD, PhD,⁷ Tamara D. Simon, MD, MSPH,⁸ Mandeep Tamber, MD, PhD,⁹ John C. Wellons III, MD, MSPH,⁴ William E. Whitehead, MD,¹⁰ and John R. W. Kestle, MD, MSc,¹¹ for the Hydrocephalus Clinical Research Network

¹Division of Neurosurgery, Hospital for Sick Children, University of Toronto, Ontario, Canada; ²Section of Neurosurgery, Alberta Children's Hospital, University of Calgary, Alberta, Canada; ³Department of Neurosurgery, Division of Pediatric Neurosurgery, The University of Alabama at Birmingham and Children's Hospital of Alabama, Birmingham, Alabama; ⁴Department of Neurological Surgery, Vanderbilt University, Nashville, Tennessee; ⁵Department of Pediatrics and ¹¹Department of Neurosurgery, University of Utah, Salt Lake City, Utah; ⁶Division of Pediatric Neurosurgery and ⁸Department of Pediatrics, Seattle Children's Hospital, Seattle, Washington; ⁷Department of Neurological Surgery, St. Louis Children's Hospital, St. Louis, Missouri; ⁹Department of Neurological Surgery, Pittsburgh Children's Hospital, Pittsburgh, Pennsylvania; and ¹⁰Department of Neurosurgery, Texas Children's Hospital, Houston, Texas

OBJECTIVE High-quality data comparing endoscopic third ventriculostomy (ETV) with choroid plexus cauterization (CPC) to shunt and ETV alone in North America are greatly lacking. To address this, the Hydrocephalus Clinical Research Network (HCRN) conducted a prospective study of ETV+CPC in infants. Here, these prospective data are presented and compared to prospectively collected data from a historical cohort of infants treated with shunt or ETV alone.

METHODS From June 2014 to September 2015, infants (corrected age ≤ 24 months) requiring treatment for hydrocephalus with anatomy suitable for ETV+CPC were entered into a prospective study at 9 HCRN centers. The rate of procedural failure (i.e., the need for repeat hydrocephalus surgery, hydrocephalus-related death, or major postoperative neurological deficit) was determined. These data were compared with a cohort of similar infants who were treated with either a shunt (n = 969) or ETV alone (n = 74) by creating matched pairs on the basis of age and etiology. These data were obtained from the existing prospective HCRN Core Data Project. All patients were observed for at least 6 months.

RESULTS A total of 118 infants underwent ETV+CPC (median corrected age 1.3 months; common etiologies including myelomeningocele [30.5%], intraventricular hemorrhage of prematurity [22.9%], and aqueductal stenosis [21.2%]). The 6-month success rate was 36%. The most common complications included seizures (5.1%) and CSF leak (3.4%). Important predictors of treatment success in the survival regression model included older age (p = 0.002), smaller preoperative ventricle size (p = 0.009), and greater degree of CPC (p = 0.02). The matching algorithm resulted in 112 matched pairs for ETV+CPC versus shunt alone and 34 matched pairs for ETV+CPC versus ETV alone. ETV+CPC was found to have significantly higher failure rate than shunt placement (p < 0.001). Although ETV+CPC had a similar failure rate compared with ETV alone (p = 0.73), the matched pairs included mostly infants with aqueductal stenosis and miscellaneous other etiologies but very few patients with intraventricular hemorrhage of prematurity.

CONCLUSIONS Within a large and broad cohort of North American infants, our data show that overall ETV+CPC appears to have a higher failure rate than shunt alone. Although the ETV+CPC results were similar to ETV alone, this comparison was limited by the small sample size and skewed etiological distribution. Within the ETV+CPC group, greater extent of CPC was associated with treatment success, thereby suggesting that there are subgroups who might benefit from the addition of CPC. Further work will focus on identifying these subgroups.

<https://thejns.org/doi/abs/10.3171/2017.8.PEDS17217>

KEY WORDS hydrocephalus; endoscopy; choroid plexus; shunt

ABBREVIATIONS CPC = choroid plexus cauterization; ETV = endoscopic third ventriculostomy; ETVSS = Endoscopic Third Ventriculostomy Success Score; FOHR = frontal and occipital horn ratio; HCRN = Hydrocephalus Clinical Research Network; IVH = intraventricular hemorrhage; TVMI = third ventricle morphology index.

SUBMITTED April 24, 2017. **ACCEPTED** August 24, 2017.

INCLUDE WHEN CITING Published online December 15, 2017; DOI: 10.3171/2017.8.PEDS17217.

ENDOSCOPIC third ventriculostomy (ETV) with the added use of choroid plexus cauterization (CPC) has been shown to have promising results in the treatment of hydrocephalus in Africa.^{10,13,14} Based on retrospective work conducted by our group and others in North America, ETV+CPC appears to be a safe procedure but with varying degrees of treatment success.^{1,7,12} It is still not firmly established which infants will benefit most from ETV+CPC and in whom it represents a reasonable alternative to the traditional CSF shunt. Here, we present the results of a prospective study within the Hydrocephalus Clinical Research Network (HCRN; *Appendix 1*) to describe the success and complications of ETV+CPC in infants and to compare results to a historical cohort of infants treated with either shunt placement or ETV alone. Uniquely, in the current multicenter prospective study, we applied a predefined consensus definition for infants with hydrocephalus who were eligible for ETV+CPC, as well as a strict definition for treatment failure.

Methods

The study population consisted of infants (corrected age ≤ 24 months) receiving treatment at 1 of 9 HCRN centers who required treatment for new-onset hydrocephalus, or failure of a previous CSF shunt, with anatomy suitable for ETV+CPC on preoperative MRI and life expectancy greater than 12 months. Suitable anatomy was defined as < 3 -mm-thick third ventricle floor, ventriculomegaly sufficient to allow safe passage of an endoscope, and the absence of marked prepontine subarachnoid adhesions on constructive interference in steady state (CISS)/fast imaging employing state-steady acquisition (FIESTA) MRI. We developed the following consensus clinical eligibility criteria for treatment: 1) presence of clear ventriculomegaly with a frontal and occipital horn ratio (FOHR)^{4,11} > 0.45 and 2) at least one of the following: head circumference > 98 th percentile for the patient's corrected age, bulging fontanelle, splayed sutures, upgaze paresis or palsy (i.e., sundowning), CSF leak, papilledema, tense pseudomeningocele or tense fluid tracking along a shunt, vomiting or irritability with no other attributable cause, bradycardias or apneas with no other attributable cause, or intracranial pressure monitoring showing persistent elevation of pressure with or without plateau waves. While surgeons followed these criteria to determine patient eligibility, exceptions could be made to include other patients at the surgeon's discretion, and this was monitored. Study consent for data collection was obtained from parents when required by the local institutional review board or research ethics board. Patient recruitment began in some centers as early as June 2014, with staggered entry of all 9 centers by October 2014.

The historical cohort consisted of similar patients (corrected age < 24 months) who were treated at the same 9 participating HCRN centers with either a shunt or ETV alone. All patients in the historical cohort had been treated before January 1, 2013. This was before ETV+CPC became popular within the HCRN, thus allowing us to identify a patient group with characteristics as similar as possible to those who would later undergo ETV+CPC. These

data were obtained from the existing HCRN Core Data Project, in which data are collected prospectively, and, for this analysis, analyzed retrospectively. For these analyses, only patients who were undergoing the first permanent treatment of hydrocephalus were included.

Intervention

The details of the ETV+CPC procedure are now widely known, practiced within the HCRN, and include the following steps: unilateral coronal entry site, fenestration of the floor of third ventricle, and attempting complete CPC of both lateral ventricles with septum pellucidotomy when needed. Although most surgeons used the flexible endoscope exclusively, a few surgeons used a rigid endoscope but almost always in combination with the flexible endoscope. Insertion of a reservoir or external ventricular drain and the use of postoperative CSF drainage (e.g., external ventricular drain, lumbar puncture) was performed at the surgeon's discretion. Detailed intraoperative data were collected at the time of surgery from the operating surgeon, including 3 different means of estimating the degree of CPC: the surgeon's estimate of CPC percentage, category of CPC percentage (0%, $< 40\%$, 40%–60%, 60%–90%, and $\geq 90\%$), and a diagrammatic representation of the amount of CPC (surgeons completed a diagram to indicate how many of the 14 sectors of the choroid plexus they successfully cauterized; the number of sectors cauterized was divided by the number of sectors in which choroid plexus was present to obtain a percentage estimate of CPC) (Fig. 1).

Follow-Up

Patients were followed per the standard of care at the HCRN centers and generally included clinical visits between 2 and 10 weeks after ETV+CPC, between 9 and 15 months after ETV+CPC, and further visits as clinically indicated; ultrasound, CT, or MRI within 30 days of ETV+CPC; MRI between 9 and 15 months after ETV+CPC; and further imaging as clinically indicated. For the purposes of this analysis, all patients were observed for at least 6 months after ETV+CPC.

Primary Outcome

The primary outcome was failure, which was defined as any one of the following: recurrence of symptomatic hydrocephalus from failure of ETV+CPC and/or the presence of loculated compartments, CSF infection, and significant intraoperative complication (including death, major postoperative neurological deficit, failure to fenestrate the floor of the third ventricle, or placement of a shunt during the planned ETV+CPC procedure). Detailed definitions of these outcomes can be found in *Appendix 2*. These definitions were agreed to a priori by consensus among the HCRN investigators.

Secondary Outcomes

A number of other outcomes were also assessed, including all major perioperative and postoperative complications and those related to CSF circulation, infection, hemorrhage, seizure, and new neurological deficit.

FIG. 1. Diagrammatic representation of the amount of CPC performed. Each of the 7 areas is meant to represent a different sector of the choroid plexus in each lateral ventricle. For each sector, the surgeon indicates if the choroid plexus in that sector was cauterized (Ct), not cauterized (NotCt), or absent (Abs). The percentage of CPC is calculated as the percentage of sectors marked Ct divided by the total number of sectors with choroid plexus.

Statistical Analysis

The primary analysis was a descriptive analysis of the time to first treatment failure (recorded from the date of surgery to the date of first failure) in the study patients, which included construction of Kaplan-Meier survival curves. Univariable Cox proportional hazards regression models were then used to determine the impact of the following independent variables on time to first treatment failure.

Preoperative Variables

Preoperative variables included patient age, etiology of hydrocephalus (categorized as myelomeningocele, intraventricular hemorrhage (IVH) of prematurity, aqueductal stenosis, or other), presence of a previous shunt, ETV Success Score (ETVSS) (categorized as ≤ 40 , 50–70, or ≥ 80),⁶ preoperative ventricle size (FOHR),^{4,11} degree of pre-pontine adhesion, and third ventricle morphology index (TVMI).²

Intraoperative Variables

Intraoperative variables included the amount of CPC actually performed (as quantified intraoperatively by the surgeon using each of the 3 methods described above), presence of residual prepontine membranes, visualization of the naked basilar artery, estimated size of the ostomy, and ballooning of the third ventricle floor after ostomy was performed.

Because we quantified the degree of CPC in 3 different ways, all 3 methods were investigated. We found that the most robust and granular method was the diagrammatic method (Fig. 1), and therefore this method was used for the final analyses. We found the rank-based (Spearman) correlation between the surgeon's estimate of CPC and the diagrammatic method to be high (0.73, $p < 0.001$). All variables that were both significant or nearly significant

($p < 0.15$) and missing less than 10% of their values were considered candidate predictors for the multivariable Cox model. The final multivariable model was constructed using a bidirectional stepwise selection process, and only variables independently associated with time to failure were kept ($p < 0.15$).

Comparison with the historical cohort was performed in 2 ways. First, each ETV+CPC patient was matched to a patient who received a shunt and a patient who underwent ETV only, with all patients in the same age category (< 1 month, 1–6 months, 6–12 months, and 12–24 months) and the same etiology category (myelomeningocele, IVH of prematurity, aqueductal stenosis, and other). These matched cohorts were then compared using Kaplan-Meier survival curves and log-rank statistics. Second, 3 pairwise stratified log-rank tests were created to compare the 3 unmatched patient cohorts (ETV+CPC vs shunt, ETV+CPC vs ETV alone, and ETV alone vs shunt) that were stratified by ETVSS (≤ 40 , 50–70, and ≥ 80).

Results

A total of 118 infants were enrolled at the 9 HCRN centers between June 2014 and September 2015. Their baseline characteristics are shown in Table 1. Of these 118 infants, 113 (96.0%) met the consensus clinical eligibility criteria for treatment. The details of the ETV+CPC procedure are shown in Table 2, and postoperative complications are shown in Table 3. The median duration of surgery was 105 minutes. The most common postoperative complication was seizure in 6 patients (5.1%). Of these 6 infants, 5 had a corrected age of less than 1 month, 5 had bleeding during surgery (4 mild and 1 severe), and the duration of surgery ranged from 61 to 141 minutes (median 99.5 minutes). Their etiologies were myelomeningocele in 3 infants and IVH of prematurity, aqueductal stenosis, and another complication in 1 infant each.

TABLE 1. Baseline characteristics of patients who underwent ETV+CPC

Characteristic	Value
No. of patients	118
Previous shunt	6 (5.1)
Corrected age at time of ETV+CPC in mos, median (IQR)	1.3 (0.1–4.7)
Corrected age at time of ETV+CPC procedure in mos	
<1	57 (48.3)
1–6	38 (32.2)
6–12	13 (11.0)
12–24	10 (8.5)
Etiology of hydrocephalus	
Myelomeningocele	36 (30.5)
IVH of prematurity	27 (22.9)
Aqueductal stenosis	25 (21.2)
Posterior fossa cyst*	9 (7.6)
Spontaneous ICH/IVH/SAH†	6 (5.1)
Communicating congenital hydrocephalus	5 (4.2)
Other congenital condition‡	3 (2.5)
Postinfectious	3 (2.5)
Post head injury	2 (1.7)
Craniosynostosis	1 (0.8)
Other etiology	1 (0.8)
Presenting signs & symptoms	
Increasing head circumference	81 (68.6)
Bulging fontanelle	79 (66.9)
Splayed sutures	61 (51.7)
Upgaze palsy	8 (6.8)
Vomiting & irritability	7 (5.9)
Bradycardia or apneas	4 (3.4)
Tense pseudomeningocele along shunt track	3 (2.5)
CSF leak	1 (0.8)
Papilledema	1 (0.8)
Preop MRI findings	
FOHR, median (IQR)	0.6 (0.5–0.7)
Prepontine adhesions§	
Few	23 (26.7)
Many	2 (2.3)
None	61 (70.9)
Aqueduct¶	
Normal	63 (53.8)
Obstructed	29 (24.8)
Narrowed	25 (21.4)
Concave floor of the 3rd ventricle**	55 (47.8)
TVMI, median (IQR)**	0.2 (0.2–0.3)
ETVSS	
0	0 (0)
10	2 (1.7)
20	0 (0)
30	37 (31.4)

CONTINUED IN NEXT COLUMN »

» CONTINUED FROM PREVIOUS COLUMN

TABLE 1. Baseline characteristics of patients who underwent ETV+CPC

Characteristic	Value
ETVSS (<i>continued</i>)	
40	40 (33.9)
50	18 (15.3)
60	6 (5.1)
70	8 (6.8)
80	7 (5.9)
90	0 (0)

ICH = intracerebral hemorrhage; IQR = interquartile range; SAH = subarachnoid hemorrhage.

Values are shown as the number of patients (%) unless indicated otherwise.

* Examples: Dandy-Walker, variants.

† Examples: arteriovenous malformation, aneurysm.

‡ Examples: schizencephaly, holoprosencephaly.

§ Data available for 86 patients.

¶ Data available for 117 patients.

** Data available for 115 patients.

A total of 76 patients (64.4%) met the primary outcome of treatment failure. The median survival after ETV+CPC was 90 days. Among those patients with failed treatment, the median time to failure was 48 days. The modes of failure are listed in Table 4. The Kaplan-Meier survival curve for time to treatment failure is shown in Fig. 2. Overall, the 6-month success rate was 36%.

Predictors of ETV+CPC Failure

The results of the univariable Cox regression analysis revealed 9 variables with $p < 0.15$ that were suitable for entry into the multivariable model: corrected age, etiology, ETVSS, preoperative ventricle size (FOHR), TVMI, the surgeon's estimate of the degree of CPC based on the diagrammatic representation, presence of prepontine residual membranes, visualization of a naked basilar artery, and ballooning of the third ventricle floor after ostomy was performed. In the multivariable Cox regression model, age, ventricle size, and degree of CPC (all analyzed as continuous variables) remained significant ($p < 0.05$) predictors of treatment success. The results of this model are shown in Table 5.

Comparison with the Historical HCRN Cohort

The historical cohort consisted of 969 infants with shunts and 74 infants with ETV alone. Using the matching algorithm, 112 ETV+CPC and shunt-matched pairs and 34 ETV+CPC and ETV alone-matched pairs were identified. The characteristics of these matched pairs are shown in Table 6. Kaplan-Meier survival curves comparing the matched cohorts are shown in Fig. 3. ETV+CPC had a shorter time to failure compared with shunts ($p < 0.001$) but not when compared with ETV alone ($p = 0.73$) using the log-rank test. The robustness of these findings was confirmed using the log-rank test and stratified by age and etiology for the entire cohort rather than restricted to the matched pairs. Both approaches produced similar results.

TABLE 2. Intraoperative details of ETV+CPC

Characteristic	Value
No. of patients	118
Type of scope	
Flexible	102 (86.4)
Rigid	3 (2.5)
Both	13 (11.0)
Septostomy	46 (39.0)
Surgeon's estimate of CPC percentage, median (IQR)*	95 (88–95)
Surgeon's estimate of CPC percentage	
0%	9 (7.6)
<40% (roughly half the choroid plexus of 1 ventricle)	2 (1.7)
40–60% (all the choroid plexus of 1 ventricle, including temporal horn)	5 (4.2)
60–90% (all of 1 ventricle, plus most of the opposite ventricle)	16 (13.6)
>90% (all of both ventricles, including the temporal horns)	86 (72.9)
Estimate of CPC percentage based on the surgeon's completed diagram	
0%	9 (7.6)
<40% of visible choroid plexus sectors	3 (2.5)
40–60% of visible choroid plexus sectors	2 (1.7)
60–90% of visible choroid plexus sectors	16 (13.6)
90% of visible choroid plexus sectors	88 (74.6)
Bleeding during procedure	
Entry into ventricle	8 (6.8)
ETV	22 (18.6)
Septostomy	5 (4.2)
Ipsilateral CPC	15 (12.7)
Contralateral CPC	19 (16.1)
Extent of bleeding during procedure	
Mild (did not obstruct view totally)	37 (31.4)
Moderate (view totally obstructed but cleared within 2–3 min)	8 (6.8)
Severe (took more than 5 mins to return to a clear working condition)	3 (2.5)
None	70 (59.3)
Forniceal injury ipsilateral	
No visible injury w/ pristine fornix	110 (93.2)
Small punctuate contusions & subpial hemorrhage w/ ependyma intact	3 (2.5)
Large confluent contusions & subpial hemorrhage w/ ependyma intact	0 (0)
Small breach of ependyma overlying the fornix	2 (1.7)
Frank tear of the fornix	0 (0)
Could not be assessed	3 (2.5)
Major arterial injury	0 (0)
Venous injury	4 (3.4)
Thalamic contusion	0 (0)
Hypothalamic contusion	1 (0.8)
Procedure abandoned	7 (5.9)

CONTINUED IN NEXT COLUMN »

» CONTINUED FROM PREVIOUS COLUMN

TABLE 2. Intraoperative details of ETV+CPC

Characteristic	Value
Procedure used to puncture floor†	
Monopolar cautery w/o cauterization	95 (81.9)
Bipolar cautery	0 (0)
Stylet	10 (8.6)
Closed forceps	6 (5.2)
Scissors	0 (0)
Monopolar cautery w/ cauterization	4 (3.4)
Endoscope	1 (0.9)
Ballooning of the 3rd ventricle floor‡	89 (77.4)
Prepontine residual membranes were not opened‡	29 (25.2)
Able to guide scope through ostomy‡	111 (96.5)
Clear view of basilar artery view‡	108 (93.9)
Lumbar or external ventricular drain used	6 (5.1)
Surgeon's estimated size of ventriculostomy in mm, median (IQR)‡	5.0 (4.0–5.0)

Values are shown as the number of patients (%) unless indicated otherwise.

* Data available for 117 patients.

† Data available for 116 patients.

‡ Data available for 115 patients.

Discussion

Our multicenter prospective study of ETV+CPC has shown that this procedure can be carried out quite safely, with low rates of intraoperative complications and with a high degree of success in obtaining a substantial amount of CPC. We also confirmed that established predictors of ETV+CPC success include older age, greater degree of CPC,^{7,14} and smaller ventricle size, which has not been consistently reported before. We also found the diagrammatic method of estimating the amount of CPC performed was valuable and could provide a standardized measuring tool in future studies.

TABLE 3. Postoperative complications

Characteristic	No. of Patients (%)
No. of patients	118
Seizure	6 (5.1)
CSF leak	4 (3.4)
Minor	3 (2.5)
Major	1 (0.8)
Postop hemorrhage	4 (3.4)
Pseudomeningocele	0 (0)
New neurological deficit	1 (0.8)
Resolved	0 (0)
Unresolved	1 (0.8)
Documented bacterial meningitis	1 (0.8)
Wound infection	0 (0)
Hyponatremia	1 (0.8)

TABLE 4. Modes of ETV+CPC failure

Mode of Failure	No. of Patients (%)
No. of patients	72
Failure of adequate CSF absorption	66 (86.8)
Presence of ≥ 1 qualifying sign or symptom & ≥ 1 positive ancillary test	60 (90.9)
No signs or symptoms, but ventricles increased in size & supratentorial subarachnoid spaces remain effaced compared w/ preop & no clinical or radiographic suggestion that atrophy was the cause	1 (1.5)
Presence of a CSF leak that did not resolve & required op revision	1 (1.5)
Clinical & op findings in the case of an emergency revision CSF diversion procedure performed w/o any ancillary tests or a revision performed prior to the 3-mo follow-up scan	4 (6.1)
Loculated compartments requiring repeat surgery	1 (1.3)
Significant intraop complication	9 (11.8)

Although our overall complication rates were low and would generally be considered acceptable, the rate of postoperative seizures was rather high (5.1%). In long-term studies of mostly shunt-treated children with hydrocephalus, the prevalence of seizures (at least 1 per year) is nearly 15%.^{3,9} Regardless, the 5.1% incidence of early postoperative seizures is worrisome and could be related to the overall extent of surgical manipulation required by the CPC component of the surgery or perhaps to the amount of irrigation required during a prolonged operation, thereby making the infant brain more susceptible to seizures. It is perhaps notable that most of the 6 children who had postoperative seizures were very young (corrected age less than 1 month) and had some evidence of bleeding during the procedure. Long-term follow-up will be necessary to

see the extent to which seizures persist in these children. This is a particularly concerning complication because previous work on hydrocephalus has shown that one of the most consistent predictors of poor quality of life is the presence of epilepsy.^{3,9}

Larger preoperative ventricle size as a predictor of ETV+CPC failure has not been widely reported before. Although this finding will need corroboration in future studies, it can be interpreted in at least one of 2 ways. On one hand, it might suggest that we are treating some patients too late to truly achieve the maximum benefit of ETV+CPC. Alternatively, it could be interpreted that some patients with smaller ventricles are being overtreated and might not have needed the procedure at all. This is a particular concern with endoscopic procedures for which there can be an

FIG. 2. Kaplan-Meier survival curve for the time to treatment failure for the prospective ETV+CPC cohort (n = 118), with time since surgery on the horizontal axis and survival probability on the vertical axis.

TABLE 5. Multivariable Cox regression model results for time to treatment failure

Variable	HR (95% CI)	p Value
Corrected age at surgery	0.87 (0.80–0.95)	0.002
Preop ventricle size	1.40 (1.09–1.80)	0.009
Surgeon's estimate of the percentage of CPC	0.24 (0.07–0.84)	0.02
Visualization of naked basilar artery	0.33 (0.10–1.10)	0.07

insidious lowering of the threshold for treatment compared with shunt placement, i.e., surgeons and families might be more willing to consider treatment with ETV+CPC in a questionably symptomatic child, whereas they would not agree to place a shunt in the same situation. We tried to mitigate this latter point by having standardized consensus clinical eligibility criteria that included a minimum degree of symptomatology and signs and at least moderate ventriculomegaly (FOHR > 0.45) to convince us that these patients were truly in need of CSF diversion. These criteria were met by 96% of our cohort.

Direct comparisons between ETV+CPC, shunting, and ETV alone in North American settings are greatly lacking. We used a matched historical control group to provide some estimate of the relative success rates of these procedures. Our matched comparison with shunting, which included 112 matched pairs, reconfirms that on average the failure rate of ETV+CPC is higher than shunting in the early postoperative phase (< 6 months). We would expect, however, that the failure curve for ETV+CPC will level off (if it is analogous to what we know about ETV),⁵ while the curve for shunting will continue to deteriorate; this will need a longer follow-up period to confirm. Despite the emerging evidence of the superiority of shunting in achieving, at least, short-term treatment success, it is our anecdotal experience that some families still prefer to attempt ETV+CPC over shunting as the initial surgical treatment for their child. This suggests that some families see inherent benefit in being shunt free and are willing to undergo a riskier surgery with a lower chance of success for the possibility of achieving this shunt freedom. This has implications about how we, as surgeons, present the treatment options to families.

Our matched comparison with ETV alone is very limited, however, because the number of patients is very small and the matched cohort consisted mostly of patients with aqueductal stenosis and other etiologies. We could only match ETV+CPC patients to those infants whom surgeons had previously and specifically selected for ETV alone. The latter is, presumably, a highly select group. As such, the matched cohort is not at all representative of a typical population of infants with hydrocephalus and, in particular, grossly underrepresents the patients most likely to benefit from CPC: infants with myelomeningocele and IVH of prematurity. These infants were virtually never offered ETV alone (e.g., there were only 3 such patients in the matched cohort). As well, given the fact that the greater extent of CPC was a predictor of ETV+CPC success, at least some infants do seem to benefit from the addition of

TABLE 6. Distribution of matched pairs for ETV+CPC with shunt or ETV alone

Etiology & Corrected Age Group	No. of Patients (%)	
	ETV+CPC & Shunt	ETV+CPC & ETV Alone
No. of pairs	112	34
IVH of prematurity	25 (22.3)	3 (8.8)
<1 mo	16 (14.3)	1 (2.9)
1–6 mos	7 (6.3)	1 (2.9)
6–12 mos	1 (0.9)	0 (0)
12–24 mos	1 (0.9)	1 (2.9)
Myelomeningocele	36 (32.1)	0 (0)
<1 mo	21 (18.8)	0 (0)
1–6 mos	12 (10.7)	0 (0)
6–12 mos	3 (2.7)	0 (0)
12–24 mos	0 (0)	0 (0)
Aqueductal stenosis	25 (22.3)	10 (29.4)
<1 mo	11 (9.8)	1 (2.9)
1–6 mos	10 (8.9)	5 (14.7)
6–12 mos	2 (1.8)	2 (5.9)
12–24 mos	2 (1.8)	2 (5.9)
Other etiology	26 (23.2)	21 (61.8)
<1 mo	9 (8.0)	4 (11.8)
1–6 mos	7 (6.3)	7 (20.6)
6–12 mos	5 (4.5)	5 (14.7)
12–24 mos	5 (4.5)	5 (14.7)

CPC. Regardless, it does beg the question of whether there are subsets of infants who might, in fact, have little to gain from the addition of CPC to ETV. As an example, the recent prospective International Infant Hydrocephalus Study reported a very high success rate for ETV alone in infants with pure aqueductal stenosis (66% success rate at 1 year), especially in those older than 6 months (80% success rate at 1 year).⁸ ETV alone might be sufficient for such a subgroup.

Conclusions

In a large, broad cohort of North American infants, our data show that overall ETV+CPC appears to have a higher failure rate than shunting. Although the ETV+CPC results were similar to ETV alone, this comparison was limited by the small sample size and skewed etiological distribution. Within the ETV+CPC group, a greater extent of CPC was associated with treatment success, thereby suggesting that there are subgroups who benefit from the addition of CPC. Further work will focus on identifying these subgroups.

Appendix 1

Hydrocephalus Clinical Research Network

Members

The HCRN currently consists of the following clinical centers and investigators: Primary Children's Hospital, University of Utah (J. Kestle); Children's of Alabama, University of Alabama at

FIG. 3. Kaplan-Meier survival curves comparing matched cohorts, with time since surgery on the horizontal axis and survival probability on the vertical axis. **Upper:** ETV+CPC and shunting (n = 112 pairs). **Lower:** ETV+CPC and ETV alone (n = 34 pairs).

Birmingham (J. Oakes, C. Rozzelle); Hospital for Sick Children, University of Toronto (J. Drake, A. Kulkarni, D. Cochrane); Texas Children's Hospital, Baylor College of Medicine (T. Luerssen, W. Whitehead); Seattle Children's Hospital, University of Washington (S. Browd, T. Simon); Children's Hospital of Pittsburgh, University

of Pittsburgh (M. Tamber); St. Louis Children's Hospital, Washington University in St. Louis (D. Limbrick); Monroe Carell Jr. Children's Hospital at Vanderbilt, Vanderbilt University Medical Center (J. Wellons, R. Naftel, C. Shannon); British Columbia Children's Hospital, University of British Columbia (P. McDonald); Alberta

Children's Hospital, University of Calgary (J. Riva-Cambrin); The Johns Hopkins Hospital (E. Ahn); Children's Hospital of Los Angeles (M. Krieger); Children's Hospital Colorado (T. Hankinson); Nationwide Children's Hospital (J. Pindrik); HCRN Data Coordinating Center, Department of Pediatrics, University of Utah (R. Holubkov).

Appendix 2

Definition of ETV+CPC Failure

1. ETV Obstruction

- The presence of at least 1 positive sign or symptom and at least 1 positive ancillary test.
 - o Symptoms: headache, nausea, vomiting, decreased level of consciousness, irritability, loss of developmental milestones.
 - o Signs: papilledema, bulging fontanelle, nuchal rigidity, sixth cranial nerve paresis, loss of upward gaze, new or increased seizures, increased head circumference, progressive pseudomeningocele.
 - o Ancillary tests
 - X CT scan, MRI, or ultrasound showing enlarged ventricles compared with the 3-month postoperative study or ventricles that have failed to decrease in size compared with the preoperative study.
 - X Intracranial pressure monitoring showing persistent elevation of pressure with or without plateau waves.
 - o Date of failure will be recorded as the date of the ancillary test.
- When 1) there are no symptoms or signs of ETV obstruction but the ventricles are increased in size and the supratentorial subarachnoid spaces remain effaced compared with preoperation and 2) there is no clinical or radiographic suggestion that atrophy is the cause, this is considered an ETV obstruction.
 - o Date of failure will be recorded as the date of the first imaging test to meet this criterion.
- A CSF leak that does not resolve and requires operative revision is considered an ETV obstruction (i.e., CSF leak that does not resolve with optimal wound revision).
 - o Date of failure will be recorded as the date of the operative revision.
- In the rare event of emergent ETV revision without any ancillary tests, or a revision performed prior to the 3-month follow-up scan, obstruction will be judged to be present or absent using clinical information and the operative findings.
 - o Date of failure will be recorded as the date of the ETV revision.

2. Loculated Compartments

- The presence of a loculated portion of a ventricular system that is enlarged more than normal, compressing the surrounding brain, and requires reoperation will be considered evidence of ETV failure and accepted as an end point for the study.
 - o Date of failure will be recorded as the date of the reoperation.

3. CSF Infection

- CSF infection will be diagnosed in the presence of 1 of the following symptoms or signs with at least 1 of the following ancillary tests:
 - o Symptoms and signs: fever, meningismus, wound erythema.
 - o Ancillary tests: culture or identification of organisms on Gram stain of CSF (or blood culture in a ventriculoatrial shunt) withdrawn under sterile conditions.
- Exposed shunt hardware.
- Abdominal pseudocyst in the presence of ventriculoperitoneal shunt.
- Date of failure will be recorded as the date of the first positive CSF specimen.

4. Significant Intraoperative Complication

- The following major intraoperative complications will be considered a failure of the procedure and will be accepted as having met the primary outcome:
 - o Mortality.
 - o Major postoperative neurological deficit.
 - o Failure to fenestrate the floor of the third ventricle or the lamina terminalis if used as an alternative or placement of shunt during the planned ETV+CPC procedure.
- Date of failure will be recorded as the date of the index ETV+CPC surgery.

Acknowledgments

The Hydrocephalus Clinical Research Network has been funded by the National Institute of Neurological Disorders and Stroke (grant no. 1RC1NS068943-01), the Patient Centered Outcome Research Institute (grant no. CER-1403-13857), The Gerber Foundation (reference no. 1692-3638), private philanthropy, and the Hydrocephalus Association. None of the sponsors participated in the design and conduct of this study; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of this manuscript. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of the sponsors.

We thank our colleagues who kindly agreed to participate in this HCRN project and allowed the collection of patient data for the purposes of this publication: D. Brockmeyer, M. Walker, R. Bollo, J. Blount, J. Johnston, B. Rocque, L. Ackapo-Satchivi, P. Dirks, J. Rutka, M. Taylor, D. Curry, R. Dauser, A. Jea, S. Lam, R. Ellenbogen, J. Ojemann, A. Lee, A. Avellino, I. Pollack, S. Greene, E. Tyler-Kabara, T. S. Park, J. Leonard, M. Smyth, N. Tulipan, A. Singhal, P. Steinbok, W. Hader, C. Gallagher, M. Benour, E. Kiehna, J. G. McComb, A. Robson, M. Handler, B. O'Neill, C. Wilkinson, L. Governale, J. Leonard, and E. Sribnick. In addition, this work would not have been possible without the outstanding support of the dedicated personnel at each clinical site and the data coordinating center. Special thanks go to J. Clawson, N. Tattersall, T. Bach (Salt Lake City); A. Arynchyna, A. Bey (Birmingham); H. Ashrafpour, L. O'Connor, (Toronto); S. Martinez, S. Ryan (Houston); A. Anderson, G. Bowen (Seattle); K. Diamond, A. Luther (Pittsburgh); D. Morales, D. Berger, D. Mercer (St. Louis); S. Gannon (Nashville); A. Cheong, R. Hengel (British Columbia); and M. Langley, V. Wall, N. Nunn, V. Freimann, and B. Miller (Utah Data Coordinating Center).

References

1. Chamiraju P, Bhatia S, Sandberg DI, Ragheb J: Endoscopic

- third ventriculostomy and choroid plexus cauterization in posthemorrhagic hydrocephalus of prematurity. **J Neurosurg Pediatr** 13:433–439, 2014
2. Foroughi M, Wong A, Steinbok P, Singhal A, Sargent MA, Cochrane DD: Third ventricular shape: a predictor of endoscopic third ventriculostomy success in pediatric patients. **J Neurosurg Pediatr** 7:389–396, 2011
 3. Kulkarni AV, Cochrane DD, McNeely PD, Shams I: Medical, social, and economic factors associated with health-related quality of life in Canadian children with hydrocephalus. **J Pediatr** 153:689–695, 2008
 4. Kulkarni AV, Drake JM, Armstrong DC, Dirks PB: Measurement of ventricular size: reliability of the frontal and occipital horn ratio compared to subjective assessment. **Pediatr Neurosurg** 31:65–70, 1999
 5. Kulkarni AV, Drake JM, Kestle JR, Mallucci CL, Sgouros S, Constantini S: Endoscopic third ventriculostomy vs cerebrospinal fluid shunt in the treatment of hydrocephalus in children: a propensity score-adjusted analysis. **Neurosurgery** 67:588–593, 2010
 6. Kulkarni AV, Drake JM, Mallucci CL, Sgouros S, Roth J, Constantini S: Endoscopic third ventriculostomy in the treatment of childhood hydrocephalus. **J Pediatr** 155:254–259, 2009.e1, 2009
 7. Kulkarni AV, Riva-Cambrin J, Browd SR, Drake JM, Holubkov R, Kestle JRW, et al: Endoscopic third ventriculostomy and choroid plexus cauterization in infants with hydrocephalus: a retrospective Hydrocephalus Clinical Research Network study. **J Neurosurg Pediatr** 14:224–229, 2014
 8. Kulkarni AV, Sgouros S, Constantini S: International Infant Hydrocephalus Study: initial results of a prospective, multicenter comparison of endoscopic third ventriculostomy (ETV) and shunt for infant hydrocephalus. **Childs Nerv Syst** 32:1039–1048, 2016
 9. Kulkarni AV, Shams I: Quality of life in children with hydrocephalus: results from the Hospital for Sick Children, Toronto. **J Neurosurg** 107 (5 Suppl):358–364, 2007
 10. Kulkarni AV, Warf BC, Drake JM, Mallucci CL, Sgouros S, Constantini S: Surgery for hydrocephalus in sub-Saharan Africa versus developed nations: a risk-adjusted comparison of outcome. **Childs Nerv Syst** 26:1711–1717, 2010
 11. O'Hayon BB, Drake JM, Ossip MG, Tuli S, Clarke M: Frontal and occipital horn ratio: A linear estimate of ventricular size for multiple imaging modalities in pediatric hydrocephalus. **Pediatr Neurosurg** 29:245–249, 1998
 12. Stone SSD, Warf BC: Combined endoscopic third ventriculostomy and choroid plexus cauterization as primary treatment for infant hydrocephalus: a prospective North American series. **J Neurosurg Pediatr** 14:439–446, 2014
 13. Warf BC: Comparison of endoscopic third ventriculostomy alone and combined with choroid plexus cauterization in infants younger than 1 year of age: a prospective study in 550 African children. **J Neurosurg** 103 (6 Suppl):475–481, 2005
 14. Warf BC, Mugamba J, Kulkarni AV: Endoscopic third ventriculostomy in the treatment of childhood hydrocephalus in Uganda: report of a scoring system that predicts success. **J Neurosurg Pediatr** 5:143–148, 2010

Disclosures

Dr. Limbrick: receives non–study-related clinical or research support from Medtronic, Inc., Karl Storz, Inc., and Microbot Medical, Inc.

Author Contributions

Conception and design: Kulkarni, Riva-Cambrin, Holubkov, Whitehead, Kestle. Acquisition of data: Kulkarni, Riva-Cambrin, Rozzelle, Naftel, Browd, Limbrick, Tamber, Wellons, Kestle. Analysis and interpretation of data: Kulkarni, Riva-Cambrin, Rozzelle, Naftel, Kestle. Drafting the article: Kulkarni, Riva-Cambrin, Kestle. Critically revising the article: Kulkarni, Riva-Cambrin, Naftel, Alvey, Reeder, Holubkov, Cochrane, Limbrick, Simon, Tamber, Wellons, Whitehead, Kestle. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Kulkarni. Statistical analysis: Kulkarni, Alvey, Reeder, Holubkov. Study supervision: Kulkarni.

Correspondence

Abhaya V. Kulkarni, Division of Neurosurgery, Hospital for Sick Children, Rm. 1503, 555 University Ave., Toronto, ON M5G 1X8, Canada. email: abhaya.kulkarni@sickkids.ca.