Predictors of success for combined endoscopic third ventriculostomy and choroid plexus cauterization in a North American setting: a Hydrocephalus Clinical Research Network study

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OBJECTIVE Endoscopic third ventriculostomy combined with choroid plexus cauterization (ETV+CPC) has been adopted by many pediatric neurosurgeons as an alternative to placing shunts in infants with hydrocephalus. However, reported success rates have been highly variable, which may be secondary to patient selection, operative technique, and/or surgeon training. The objective of this prospective multicenter cohort study was to identify independent patient selection, operative technique, or surgical training predictors of ETV+CPC success in infants.

METHODS This was a prospective cohort study nested within the Hydrocephalus Clinical Research Network's (HCRN) Core Data Project (registry). All infants under the age of 2 years who underwent a first ETV+CPC between June 2006 and March 2015 from 8 HCRN centers were included. Each patient had a minimum of 6 months of follow-up unless censored by an ETV+CPC failure. Patient and operative risk factors of failure were examined, as well as formal ETV+CPC training, which was defined as traveling to and working with the experienced surgeons at CURE Children's Hospital of Uganda. ETV+CPC failure was defined as the need for repeat ETV, shunting, or death.

RESULTS The study contained 191 patients with a primary ETV+CPC conducted by 17 pediatric neurosurgeons within the HCRN. Infants under 6 months corrected age at the time of ETV+CPC represented 79% of the cohort. Myelomeningocele (26%), intraventricular hemorrhage associated with prematurity (24%), and aqueductal stenosis (17%) were the most common etiologies. A total of 115 (60%) of the ETV+CPCs were conducted by surgeons after formal training. Overall, ETV+CPC was successful in 48%, 46%, and 45% of infants at 6 months, 1 year, and 18 months, respectively. Young age (< 1 month) (adjusted hazard ratio [aHR] 1.9, 95% CI 1.0–3.6) and an etiology of post-intraventricular hemorrhage secondary to prematurity (aHR 2.0, 95% CI 1.1–3.6) were the only two independent predictors of ETV+CPC failure. Specific subgroups of ages within etiology categories were identified as having higher ETV+CPC success rates. Although training led to more frequent use of the flexible scope ($p < 0.001$) and higher rates of complete (> 90%) CPC ($p < 0.001$), training itself was not independently associated (aHR 1.1, 95% CI 0.7–1.8; $p = 0.63$) with ETV+CPC success.

CONCLUSIONS This is the largest prospective multicenter North American study to date examining ETV+CPC. Formal ETV+CPC training was not found to be associated with improved procedure outcomes. Specific subgroups of ages within specific hydrocephalus etiologies were identified that may preferentially benefit from ETV+CPC.

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KEYWORDS endoscopic third ventriculostomy combined with choroid plexus cauterization; ETV+CPC; predictors; Hydrocephalus Clinical Research Network; HCRN; hydrocephalus

ABBREVIATIONS aHR = adjusted hazard ratio; CCC = complex chronic condition; CCHU = CURE Children's Hospital of Uganda; DCC = Data Coordinating Center; ETV+CPC = endoscopic third ventriculostomy combined with choroid plexus cauterization; ETVSS = ETV Success Score; EVD = external ventricular drain; FOR = frontal/occipital horn ratio; HCRN = Hydrocephalus Clinical Research Network; IVH = intraventricular hemorrhage.

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IN 2005, Warf published a seminal study, based on his work at CURE Children's Hospital of Uganda (CCHU), describing the use of the endoscopic third ventriculostomy combined with choroid plexus cauterization (ETV+CPC) for the treatment of hydrocephalus in infants.¹⁹ This surgical technique continues to grow in popularity in both the African and the North American settings.⁴ One driver for this expansion is the broadening of criteria for patients to be selected for ETV+CPC. In the original publication, 71% of infants had postinfectious or myelomeningocele etiologies for hydrocephalus.¹⁹ However, patient selection has evolved to include intraventricular hemorrhage (IVH) secondary to prematurity,^{3,8,18} Dandy-Walker syndrome,²⁵ congenital communicating hydrocephalus,^{8,20} and encephaloceles.²¹

Prior to this current study, the impact of ETV+CPC patient selection on procedural success had not yet been fully elucidated, with recent publications showing divergent results.^{1,2,8,16,22–24} In the North American setting, Stone and Warf published an overall ETV+CPC success rate of 57% and a 65% shunt-free rate in 91 infants with hydrocephalus.¹⁶ Other single-center studies without affiliation with CCHU have reported significantly lower success rates of 37%–42%.^{3,23} The Hydrocephalus Clinical Research Network (HCRN) itself has previously published studies demonstrating varying overall ETV+CPC success rates. Originally, the HCRN published a retrospective 7-center study ($n = 36$) that found a more moderate 52% overall success rate at 6 months before any formal training relationship with CCHU.⁸ More recently, the HCRN published a 9-center prospective cohort study ($n = 118$) revealing a significantly lower 36% overall success rate at 6 months.¹⁰ Therefore, it remains unclear whether these highly variable ETV+CPC success rates are associated with patient selection, operative technique, and/or surgeon training.

The objective of this prospective cohort study was to identify independent patient selection, operative technique, or surgical training predictors of ETV+CPC success in the infant hydrocephalus population. This HCRN study represents the largest multicenter study of ETV+CPC ever conducted in a North American setting.

Methods

Study Population

The study included all infants (age < 2 years) treated with an ETV+CPC procedure for hydrocephalus between June 9, 2006, and March 1, 2015, at 8 participating HCRN centers. Included infants could have had an ETV+CPC either as a first procedure after initial diagnosis or secondarily after a failed CSF shunt. No hydrocephalus etiologies were explicitly excluded because the decision to offer ETV+CPC was made entirely by the treating pediatric neurosurgeon. The participating centers within the HCRN for this specific study were as follows: the University of Utah/Primary Children's Hospital; the University of Alabama at Birmingham/Children's Hospital of Alabama; the University of Toronto/Hospital for Sick Children; the University of Washington/Seattle Children's Hospital; Baylor College of Medicine/Texas Children's Hospital; the University of Pittsburgh/Children's Hospital of Pittsburgh of

the University of Pittsburgh Medical Center; Washington University/St. Louis Children's Hospital; and Vanderbilt University/Monroe Carell Jr. Children's Hospital at Vanderbilt. A minimum of 6 months of follow-up was required for entry into the study.

Data Collection and Management

The study combined two data sources—a prospective cohort and a retrospective cohort. The majority (96%) of the 191 infants were recruited via the prospective cohort study nested within the HCRN's Core Data Project or registry. In an attempt to capture every ETV+CPC ever performed at the 8 participating centers and to maximize the heterogeneity of patient selection and surgeon experience, the study cohort was supplemented by the addition of 8 (4%) infants not originally enrolled within this prospective study (i.e., ETV+CPC before the inception of the prospective study/registry). Therefore, all 36 of the patients from Kulkarni et al. for the HCRN (2014) are represented in this study—8 fully abstracted retrospectively and 28 who were prospectively enrolled in this nested registry study but supplemented with retrospective data collection of CPC details.⁸ This patient cohort predated and was completely exclusive of the HCRN's recently published prospective cohort study.¹⁵

The study was approved by the institutional review board or research ethics board at each participating site as well as for the Data Coordinating Center (DCC) at the University of Utah. A waiver of consent was granted for the DCC and 6 centers, whereas 2 study sites required patient/parental informed consent before enrollment in the Core Data Project. For the prospective cohort, data were collected by a dedicated HCRN research coordinator in the operating room, clinic, and ward settings. For the retrospective cohort, data were abstracted from electronic and paper patient medical charts and imaging records.⁸ De-identified data were then uploaded to a secure server at the DCC and were systematically queried for data quality.

Patient Selection Variables

Patient age at ETV+CPC surgery was presented as corrected age after 40 weeks' gestation to adjust for premature birth, and was reported in months (categorically) and weeks (continuously). Corrected age was categorized into < 1 month, 1–5 months, 6–11 months, and ≥ 1 year to be consistent with the ETV Success Score (ETVSS) and previous publications.^{9,10} Hydrocephalus etiology was assigned prospectively (in the prospective cohort) by the treating surgeon into one of 16 etiologies previously described by the HCRN.¹³ In the retrospective cohort, etiology was assigned via review of the neurosurgical medical record and imaging. For meaningful analysis, these etiologies were collapsed into the most prevalent categories—myelomeningocele, post-IVH secondary to prematurity, aqueductal stenosis, and other. Comorbidities were collected using the pediatric complex chronic condition (CCC) methodology⁵ excluding hydrocephalus.^{13,14} The ventricle size at the last imaging (CT or MRI) before ETV+CPC was measured using the frontal/occipital horn ratio (FOR).¹¹ Midline sagittal series of these images were also examined to deter-

mine whether the floor of the third ventricle was normal or concave. Sex, race, insurance classification, ETVSS, and head circumference percentile corrected for age were also collected.

Operative Technique Variables

Duration of surgery was recorded in minutes and was defined as the time between the first incision and final skin closure. Surgical priority (elective, add-on, or emergency) was recorded per the actual booking by the attending surgeon. The percentage of CPC of the lateral ventricles was grossly estimated by the surgeon in a nonvalidated manner and dichotomized into $> 90\%$ and $\leq 90\%$.⁸ The “use of navigation” variable included either intraoperative ultrasound or frameless stereotaxy, primarily for entrance into the lateral ventricle. Procedures were deemed to be abandoned when the neurosurgeon did not complete the ETV or attempt any CPC, either due to anatomical considerations or secondary to complications such as hemorrhage. Other operative variables that were collected included whether the floor of the third ventricle ballooned up after ventriculostomy creation, presence of residual (i.e., unfenestrated) membranes in the prepontine cistern, an associated biopsy, the use of the flexible versus the rigid endoscope, whether the scope was guided through the ventriculostomy, whether a “naked” basilar artery was observed beneath the ventriculostomy,⁹ the surgeon’s estimate of the final size of the ventriculostomy in millimeters, and whether an external ventricular drain (EVD) was left after the procedure.

Complications were collected in a standardized fashion and divided into surgical complications (e.g., new neurological deficits, procedure-related hemorrhage, CSF leaks) and medical complications (e.g., hyponatremia, pneumonia). These were further divided into two timing categories, including those complications occurring in the immediate inpatient setting before discharge, and those occurring in a delayed fashion in individuals who were outpatients after hospital discharge.

“Formally Trained” Versus “Formally Untrained” ETV+CPC

Each ETV+CPC procedure was dichotomized into either a so-called formally trained or a formally untrained procedure. A formally trained procedure was defined as one conducted by a pediatric neurosurgeon who, before the procedure, had traveled to CCHU in Mbale, Uganda, and had formally trained with this group specifically for ETV+CPC. Formally untrained procedures were those conducted by pediatric neurosurgeons who, at the time of the procedure, had not traveled for training at CCHU. This included surgeons who had never traveled to CCHU or surgeons performing procedures before their training at CCHU.

Formal training at CCHU consisted of a 1-week visit with active participation in all aspects of the perioperative management of infant hydrocephalus, including ETV+CPC intraoperative technique. All surgeons obtained Ugandan medical licenses to allow them to fully participate in all phases of care. During the week of train-

ing, each surgeon performed at least 10 ETV+CPC procedures.

Study Outcomes

The primary outcome of this study was time to ETV+CPC failure. ETV+CPC failure was defined as patient death, ETV+CPC abandonment, or the need for a subsequent CSF diversion surgery including the placement of a CSF shunt or an ETV revision. All ETV+CPC survival data were censored on May 31, 2015, for analysis. The data were also analyzed using formally trained versus formally untrained ETV+CPC procedures as a secondary outcome to determine whether there were significant differences in patient selection or surgical techniques associated with formal training at CCHU.

Statistical Analyses

Continuous variables were reported as means $\pm$ SDs except for corrected age in weeks, which was reported as a median with minimum and maximum values. Categorical variables were reported as frequencies and percentages. Patient selection and operative technique variables (see Table 3) were compared with the primary outcome of time to ETV+CPC failure by using univariable Cox proportional hazards modeling. Significant ($p < 0.05$: corrected age, etiology, and FOR) and near-significant ($p < 0.10$: training and use of the flexible scope) variables were included in the multivariable Cox proportional hazards model. Significant (and near-significant) variables identified by the multivariable modeling were reported as the hazard ratio (HR) with 95% confidence intervals (CIs). No violations of the proportional hazards assumptions were found.

We then used the two variables that were found to have independent and significant (and near-significant) associations with ETV+CPC failure (age and etiology categories) to identify specific patient groups with the highest probability for ETV+CPC success. Therefore, Kaplan-Meier curves were generated for each collapsed etiology category (myelomeningocele, post-IVH secondary to prematurity, aqueductal stenosis, and other), which were stratified by age category.

The secondary analyses comparing formally trained and formally untrained procedures consisted of Student t-tests for continuous variables and Mantel-Haenszel chi-square and Fisher’s exact tests for categorical variables. All analyses were conducted by SAS (version 9.4, SAS Institute).

Results

We enrolled 191 infants with hydrocephalus into the study; these patients had undergone a first ETV+CPC conducted by one of 17 pediatric neurosurgeons at 8 participating centers. Figure 1 demonstrates the rapid escalation of ETV+CPC within the HCRN, especially since 2011. A total of 167 of the ETV+CPCs were first CSF diversion procedures, and 24 followed a shunt failure. A total of 183 (96%) patients were enrolled prospectively and 8 (4%) were captured retrospectively. The median corrected age at the time of the procedure was 6.3 weeks, but ranged from –6.6 to 92.7 weeks old at ETV+CPC (Table 1). There

FIG. 1. A histogram demonstrating the incidence of ETV+CPCs conducted within the HCRN by year of study.

was a predominance of males (65%) in the cohort, and 46% had a CCC other than hydrocephalus. The most common hydrocephalus etiologies were myelomeningocele (26%), post-IVH secondary to prematurity (24%), aqueductal stenosis (17%), spontaneous intracranial hemorrhage (7%), congenital communicating hydrocephalus (6%), and a variety of others including postinfectious and intracranial cysts. In terms of imaging, the mean FOR was 0.59, representing severe ventriculomegaly.⁶

The mean duration of the ETV+CPC procedure was 107 minutes and ranged from 40 to 299 minutes. Sixty percent of procedures were done following formal training, 73% using the flexible endoscope, and 73% reported > 90% CPC (Table 2).

Combining age, etiology, and prior shunting, the cohort had a mean ETVSS⁷ of 46, compared with a 48% success rate at 6 months. Overall, ETV+CPC was successful in 48%, 46%, 45%, and 44% of infants at 6 months, 1 year, 18 months, and 2 years, respectively. In terms of follow-up, all patients had follow-up at 6 months, 79% at 12 months, 57% at 18 months, and 33% at 2 years.

Univariable Associations With ETV+CPC Failure

Table 3 demonstrates each clinical and operative variable tested univariably versus the primary outcome of time to ETV+CPC failure. Corrected age category was significantly associated with time to ETV+CPC failure ($p = 0.026$). Infants 1–5 months of age (HR 1.6, 95% CI 0.9–3.0) and those < 1 month of age (HR 1.9, 95% CI 1.1–3.6) had a trend toward a significantly higher hazard of ETV+CPC failure, respectively (Fig. 2). Greater preoperative ventricle size (i.e., FOR) (HR 6.9, 95% CI 1.3–37.9; $p = 0.027$) and hydrocephalus etiology ($p = 0.001$) were also univariably associated with time to ETV+CPC failure. Specifically, patients with the post-IVH secondary to prematurity etiology had much higher ETV+CPC failure (HR 2.3, 95% CI 1.3–4.2) (Fig. 3). The use of the flexible scope (HR 1.5, 95% CI 0.9–2.4; $p = 0.095$) and formally trained procedures (HR 1.4, 95% CI 0.9–2.1; $p = 0.089$) were associated with a trend toward ETV+CPC failure. A high degree (> 90%) of CPC, residual prepontine membranes,

TABLE 1. Overall description of the patient selection variables within the HCRN's ETV+CPC cohort

Patient Selection Variables	Study Cohort, n = 191
Corrected age	
<1 mo	86 (45.0)
1–5 mos	64 (33.5)
6–11 mos	30 (15.7)
≥1 yr	11 (5.8)
Median corrected age in wks; min, max	6.3; –6.6, 92.7
Male sex	125 (65.4)
Race	
Asian	2 (1.0)
Black or African American	33 (17.3)
White	137 (71.7)
Other/unknown	19 (9.9)
Primary payer	
Public	95 (49.7)
Private	87 (45.5)
Other	9 (4.7)
Etiology	
Postinfectious	8 (4.2)
Post-IVH secondary to prematurity	46 (24.1)
Myelomeningocele	49 (25.7)
Aqueductal stenosis	33 (17.3)
Spontaneous ICH	14 (7.3)
Tumors	5 (2.6)
Post-head injury	3 (1.6)
Encephalocele	1 (0.5)
Posterior fossa cysts	5 (2.6)
Other intracranial cysts	6 (3.1)
Congenital communicating hydrocephalus	11 (5.8)
Other congenital; e.g., holoprosencephaly	2 (1.0)
Craniosynostosis	2 (1.0)
Other	6 (3.1)
≥1 CCC	87 (45.5)
Cardiac CCC	34 (17.8)
Head circumference %ile, mean ± SD*	84.5 ± 28.4
FOR, mean ± SD†	0.59 ± 0.11
Shape of 3rd ventricle floor	
Normal	91 (47.6)
Concave; down	47 (24.6)
Not available	53 (27.7)
ETVSS, mean ± SD	46.1 ± 13.9

ICH = intracranial hemorrhage; max = maximum; min = minimum.

Unless otherwise indicated, values are expressed as the number of patients (%).

* Based on 162 patients with recorded head circumference.

† Based on 189 patients with suitable imaging.

and ventricle size did not have an association with time to ETV+CPC failure. The HCRN previously found that a cardiac comorbidity was associated with time to shunt failure.¹⁴ However, this association was not identified in

TABLE 2. Overall description of the operative technique variables within the HCRN's ETV+CPC cohort

Operative Technique Variables	Study Cohort, n = 191
Duration of op in mins, mean $\pm$ SD*	106.9 $\pm$ 39
Surgical priority	
Elective	140 (73.3)
Add-on	46 (24.1)
Emergency	5 (2.6)
Conducted by trained surgeon	115 (60.2)
Flexible scope	140 (73.3)
>90% of CPC	140 (73.3)
Use of navigation	62 (32.5)
Biopsy during same op	0 (0)
Abandoned procedure	1 (0.5)
Ballooning of floor of 3rd ventricle†	161 (85.2)
Residual prepontine membranes‡	32 (16.9)
Endoscope guided through ventriculostomy‡	178 (93.7)
Naked basilar view‡	174 (91.6)
Size of ventriculostomy in mm, mean $\pm$ SD†	4.9 $\pm$ 1.3
EVD inserted‡	14 (7.4)

Unless otherwise indicated, values are expressed as the number of patients (%).

* Based on n = 185; 6 patients had missing data.

† Based on n = 189; 2 patients had missing data.

‡ Based on n = 190; 1 patient had missing data.

the current study's ETV+CPC sample ($p = 0.79$), despite a higher incidence of both overall comorbidities (46% vs 30%) and specifically a cardiac comorbidity (18% vs 8%).

Multivariable Associations With ETV+CPC Failure

Significant (corrected age, preoperative FOR, and etiology) and near-significant (formally trained vs formally untrained procedures and the use of the flexible scope) variables on univariable testing were entered into a multivariable Cox proportional hazards model comparing them with time to ETV+CPC failure. Only corrected age < 1 month (adjusted HR [aHR] 1.9, 95% CI 1.0–3.6) and the post-IVH secondary to prematurity etiology (aHR 2.0, 95% CI 1.1–3.6) were found to be independent predictors of ETV+CPC failure. Ventricle size, formally trained procedures, and the use of the flexible scope were not independently predictive (Table 3).

Relationships Between Age and Etiology as They Pertain to ETV+CPC Failure

Given that corrected age ($p = 0.078$) and etiology ($p = 0.007$) appeared significant as categories, we further stratified each etiology by corrected age while examining the relationship with time to ETV+CPC failure (Fig. 4). For myelomeningocele, success rates at 1 year were 48%, 62%, 100%, and 100% for age categories < 1 month, 1–5 months, 6–11 months, and ≥ 1 year, respectively (Fig. 4A). For post-IVH secondary to prematurity, success rates at 1 year were 9%, 28%, 75%, and 0% for corrected age categories < 1 month, 1–5 months, 6–11 months, and ≥ 1 year, respectively (Fig. 4B). For aqueductal stenosis, suc-

cess rates at 1 year were 32%, 60%, 83%, and 100% for age categories < 1 month, 1–5 months, 6–11 months, and ≥ 1 year, respectively (Fig. 4C). For the heterogeneous “other” category, success rates at 1 year were 49%, 46%, 49%, and 100% for age categories < 1 month, 1–5 months, 6–11 months, and ≥ 1 year, respectively (Fig. 4D).

Effects of Formal Training on ETV+CPC Patient Selection and Technique

Pediatric neurosurgeons with formal training at CCHU were more likely to offer ETV+CPC to younger children, especially to those < 1 month of age ($p = 0.026$) (Table 4). However, there were no differences in patient selection in regard to hydrocephalus etiology, comorbidities, or preoperative ventricle size associated with formal training. Training did significantly affect ETV+CPC surgical technique because formally trained procedures were longer ($p = 0.03$), more likely to use the flexible endoscope (94% vs 42%, $p < 0.001$), more likely to report > 90% CPC (91% vs 46%, $p < 0.001$), and less likely to leave an EVD (1% vs 17%, $p < 0.001$). There was no statistical difference in time to failure for formally trained ETV+CPC procedures versus formally untrained procedures ($p = 0.63$; see Table 3); however, in our cohort, 60% of the formally trained and 48% of the formally untrained procedures failed by 2 years. Furthermore, formally trained procedures were significantly more likely to be rescued with a repeat ETV as opposed to shunting (33% vs 10%, $p = 0.01$) than formally untrained procedures (Table 4).

Complications of ETV+CPC

Intraoperative and postoperative complications of the ETV+CPC procedures are presented in Table 5. We have data for 180 (94%) infants in regard to inpatient complications and before discharge. We found a 3.9% rate of moderate to severe intraoperative hemorrhage, a 1.7% rate of seizures, and a 3.4% CSF leak, of which only 1 case required return to surgery.

Discussion

To our knowledge, this multicenter study represents the largest North American investigation of ETV+CPC for the treatment of infant hydrocephalus. Throughout the 8 participating centers within the HCRN, we found an overall ETV+CPC success rate of 48% at 6 months and 44% at 2 years from 2006 through 2015. Univariable and multivariable Cox proportional hazards modeling found that corrected age and etiology were the only variables to predict time to ETV+CPC failure. Although formal training at the high-volume CCHU was associated with more extensive CPC and a willingness to offer ETV+CPC to younger infants, there was no benefit in terms of procedural success.

The Investigator Committee of the HCRN, through consensus, chose a success rate of $\geq 40\%$ as a cutoff to identify specific subpopulations of infant hydrocephalus that may preferentially benefit from ETV+CPC. Using this criterion, we found that all infants with myelomeningocele, infants older than 1 month corrected age with aqueductal stenosis, and those older than 6 months corrected age with the post-IVH secondary to prematurity etiology may be

TABLE 3. Comparing clinical and operative variables versus time to ETV+CPC failure

Clinical or Operative Variable	Unadjusted HR w/ 95% CIs	Cox Proportional Hazards p Value		aHR w/ 95% CIs
		Univariable	Multivariable	
Clinical variables				
Corrected age		0.026	0.078	
<1 mo	1.9 (1.1–3.6)			1.9 (1.0–3.6)
1–5 mos	1.6 (0.9–3.0)			1.6 (0.8–3.0)
6–11 mos	Reference			Reference
≥1 yr	0.4 (0.1–1.6)			0.4 (0.1–2.0)
Male sex	1.1 (0.7–1.6)	0.73	—	—
White race	0.8 (0.5–1.2)	0.26	—	—
Collapsed etiology		0.001	0.007	
Post-IVH secondary to prematurity	2.3 (1.3–4.2)			2.0 (1.1–3.6)
Myelomeningocele	1.0 (0.5–1.9)			0.9 (0.4–1.7)
Aqueductal stenosis	Reference			Reference
Other etiology	1.1 (0.6–2.0)			1.1 (0.6–2.0)
≥1 comorbidity	0.9 (0.6–1.3)	0.53	—	—
Head circumference %ile	1.0 (0.9–1.0)	0.75	—	—
FOR	6.9 (1.3–37.9)	0.027	0.17	3.9 (0.6–28.0)
Concavity of floor of 3rd ventricle	0.7 (0.4–1.2)	0.20	—	—
Operative variables				
Conducted by trained surgeon	1.4 (0.9–2.1)	0.089	0.63	1.1 (0.7–1.8)
Flexible scope	1.5 (0.9–2.4)	0.095	0.43	1.3 (0.7–2.2)
>90% CPC	1.0 (0.6–1.5)	0.94	—	—
Use of navigation	0.9 (0.6–1.3)	0.43	—	—
Ballooning of floor of 3rd ventricle	0.9 (0.5–1.5)	0.64	—	—
Residual prepontine membranes	1.5 (0.9–2.3)	0.11	—	—
Endoscope guided through ventriculostomy	1.2 (0.5–2.7)	0.66	—	—
Naked basilar view	0.6 (0.3–1.2)	0.16	—	—
Size of ventriculostomy in mm	0.9 (0.8–1.1)	0.37	—	—
EVD inserted	1.3 (0.7–2.6)	0.47	—	—

— = not applicable.

Boldface type indicates significant ($p < 0.05$) and near-significant ($p < 0.10$) values. **FIG. 2.** A Kaplan-Meier plot of all ETV+CPCs conducted during the study, with the outcome of time to failure stratified by corrected age category: < 1 month, 1–5 months, 6–11 months, and ≥ 1 year. Figure is available in color online only. **FIG. 3.** A Kaplan-Meier plot of all ETV+CPCs conducted during the study, with the outcome of time to failure stratified by hydrocephalus cause category: post-IVH secondary to prematurity, myelomeningocele, aqueductal stenosis, and other causes. Figure is available in color online only.

FIG. 4. Kaplan-Meier plots of subsamples of the ETV+CPC cohort each representing a single hydrocephalus cause, with the outcome of time to failure and stratified by corrected age category (< 1 month, 1-5 months, 6-11 months, and ≥ 1 year). **A:** Myelomeningocele. **B:** Post-IVH secondary to prematurity. **C:** Aqueductal stenosis. **D:** Other etiologies. Figure is available in color online only.

the best candidates in whom to consider ETV+CPC as a surgical option.

Overall ETV+CPC Success Rate

Our success rate in this study was 48% at 6 months and 44% at 2 years. This success is higher than the HCRN's own previous prospective study (representing patients from 2014 to 2016), in which we found a 36% success rate at 6 months.¹⁰ Both studies had very similar populations in terms of age and etiology, but Kulkarni et al. prospectively applied a stringent definition of failure after 2014, which the current study did not. This may be critically important considering the results of Dewan et al., in which the determination of failure was found to be complex and was frequently "made in the setting of discordant data."⁴ The current study's results are comparable to our previous multicenter retrospective study, which found a 52% success rate, but these patients were incorporated into the current study.⁸ In terms of other groups, our success rate was higher than that of Weil et al.,²³ who reported a 42% success at 6 months and 37% overall at a single center. One hypothesis for our marginally better success from this group might be the more prevalent use of the flexible scope versus the rigid scope. However, this study did not find the use of the flexible scope to be independently predictive of failure, and previous work has not found the rigid scope to be demonstrably inferior.¹⁸ Both Stone and

Warf¹⁶ in a single-center North American setting (57% success at 1 year) and Warf¹⁹ in an African setting (66% overall success) reported a significantly higher ETV+CPC success. This discrepancy may be due to patient selection or technical competence, because both of those reports represent results from the originator of and most experienced surgeon with ETV+CPC—Dr. Warf—who personally supervised the formal training described in this study.

Age, Hydrocephalus Etiology, and Degree of CPC as Predictors of ETV+CPC Success

Both age¹³ and etiology^{15,17} have long been cited as independent predictors of CSF diversion success, especially regarding CSF shunts. They are also both integral to ETV (without CPC) success and are included in the validated ETVSS.⁷ Therefore, it should not be surprising that they were the dominant predictors of ETV+CPC success found in this study. However, it is interesting that other published predictors of ETV+CPC were not found to be significant in this study, which has a large and diverse sample. The degree of CPC (> 90% vs ≤ 90%) has been found to be associated with ETV+CPC success¹² in 2 previous HCRN studies—univariably in the HCRN's retrospective study ($p = 0.05$)⁸ and multivariably in Kulkarni et al.¹⁰ ($p = 0.02$). The difference might lie in either this study's higher power or the Kulkarni et al. study's more sophisticated and structured method of quantifying CPC.

TABLE 4. Differences between “trained” and “untrained” procedures

Variables	Untrained ETV+CPC, n = 76	Trained ETV+CPC, N = 115	Univariable Association (p value)
Patient characteristics			
Corrected age			0.026*
<1 mo	28 (36.8)	58 (50.4)	
1–5 mos	26 (34.2)	38 (33.0)	
6–11 mos	16 (21.1)	14 (12.2)	
≥1 yr	6 (7.9)	5 (4.3)	
Collapsed etiology			0.90†
Post-IVH secondary to prematurity	17 (22.4)	29 (25.2)	
Myelomeningocele	19 (25.0)	30 (26.1)	
Aqueductal stenosis	15 (19.7)	18 (15.7)	
Other etiology	25 (32.9)	38 (33.0)	
Male sex	48 (63.2)	77 (67.0)	0.64†
≥1 CCC	37 (48.7)	50 (43.5)	0.55†
OFC %ile, mean ± SD	84.0 ± 28.4	84.8 ± 28.5	0.87‡
FOR, mean ± SD	0.60 ± 0.12	0.60 ± 0.10	0.74‡
Procedural characteristics			
Duration of op in mins, mean ± SD	98.6 ± 42.6	111.9 ± 35.5	0.030‡
Use of navigation	37 (48.7)	25 (21.7)	<0.001†
Flexible scope	32 (42.1)	108 (93.9)	<0.001†
>90% of CPC	35 (46.1)	105 (91.3)	<0.001†
Size of ventriculostomy in mm, mean ± SD	4.9 ± 1.4	4.9 ± 1.2	0.84‡
Residual prepontine membranes	17 (22.4)	15 (13.0)	0.12†
EVD inserted	13 (17.1)	1 (0.9)	<0.001†
Re-treatment modality after ETV+CPC failure§			0.010†
Repeat ETV	4 (10.3)	23 (33.3)	
CSF shunt	35 (89.7)	46 (66.7)	

OFC = occipital frontal circumference.

“Untrained” procedures refers to those done by neurosurgeons either who had never gone to CCHU or prior to their training at CURE; “trained” procedures refers to those done by neurosurgeons after training at CURE. Unless otherwise indicated, values are expressed as the number of patients (%). Boldface type indicates significant values.

* Mantel-Haenszel chi-square test.

† Fisher's exact test.

‡ Two-sided t-test with unpooled variance.

§ Percentages are of those who had a successfully completed ETV+CPC procedure that eventually failed (i.e., was not abandoned).

Identification of Specific Subpopulations of Infant Hydrocephalus for ETV+CPC

As noted above, reported ETV+CPC success rates vary significantly, from 36% to 66%,^{4,8,10,16,18,19,23} perhaps indicating that patient selection may be confounding. This study was designed to cast the widest net over the HCRN's multicenter experience to detect subpopulations that may differentially benefit from ETV+CPC. Using a combination of age and etiology similar to that found within the ETVSS,⁷ we have generated several subpopulations with the hypothesis that they may specifically benefit from this procedure—including most infants with myelomeningocele, those > 1 month corrected age with aqueductal stenosis, and the rare infants in the post-IVH secondary to prematurity subpopulation who require CSF diversion after 6 months corrected age. These findings may serve as general guidelines for future management and can help define the appropriate eligibility criteria for future randomized com-

parisons of ETV+CPC and CSF shunting in the infant hydrocephalus population.

Formal Training and ETV+CPC Success

For this study, formal training was defined by the surgeon traveling and working at CCHU in Mbale, Uganda, which is the original and highest-volume center of excellence for ETV+CPC. We found that formal training did influence surgical technique, including longer surgery, less frequent use of navigation, more frequent use of the flexible endoscope, infrequent EVD usage, and more extensive CPC. However, these technical changes did not translate into improved ETV+CPC success. This discrepancy is probably explained by our finding that patient selection is the major driver of ETV+CPC success rather than specific technical idiosyncrasies or possibly by the fact that all of the involved surgeons were already very experienced at neuroendoscopy. It is important to note that formal train-

TABLE 5. The incidence of ETV+CPC immediate and short-term complications

Complication	Immediate Inpatient Complications, n = 180	Delayed Outpatient Complications, n = 96
Surgical		
Major arterial injury*	0 (0)	NA
Hemorrhage during procedure*		NA
None	111 (61.7)	
Mild; nonobstructive	62 (34.4)	
Moderate; obstructive <5 mins	6 (3.3)	
Severe; obstructive ≥5 mins	1 (0.6)	
Postop hemorrhage		
IVH	3 (1.7)	0 (0)
ICH/SDH/EDH	0 (0)	0 (0)
New neurological deficit	1 (0.6)	1 (1.0)
New seizure	3 (1.7)	0 (0)
CSF leak		
Minor; suture	5 (2.8)	1 (1.0)
Major; return to OR	1 (0.6)	1 (1.0)
Pseudomeningocele	0 (0)	1 (1.0)
Subdural hygroma	2 (1.1)	1 (1.0)
Wound infection	0 (0)	1 (1.0)
Bacterial meningitis	0 (0)	0 (0)
Medical		
Hyponatremia	2 (1.1)	0 (0)
Urinary tract infection	3 (1.7)	0 (0)
Sepsis	0 (0)	0 (0)
Pneumonia	1 (0.6)	0 (0)
Cardiac arrest	0 (0)	0 (0)
DVT/PE	0 (0)	0 (0)
Pressure sores	1 (0.6)	0 (0)

DVT = deep venous thrombosis; EDH = epidural hemorrhage; NA = not applicable; OR = operating room; PE = pulmonary embolism; SDH = subdural hemorrhage.

Values are expressed as the number of patients (%).

* Based on a total of 191 patients.

ing did significantly lead to more rescue ETVs after failed ETV+CPCs ($p = 0.01$), indicating that if the outcome of interest for patients is shunt freedom, our results and formal training might look more promising, as suggested by Stone and Warf.¹⁶

Limitations of the Study

The largest limitation of the study is that our definition of failure, besides death or immediate ETV+CPC abandonment, was that the decision about the need for a subsequent ETV or shunt was entirely left up to the treating surgeon and was open to subjectivity. Although the vast majority of previously published CSF diversion studies have used this definition of failure, generalizability between centers and surgeons cannot be guaranteed. Therefore, in response to this limitation, the HCRN (unfortunately after this study's

completion) developed more objective criteria, which can be found in Appendix 2 of our subsequent prospective ETV+CPC study.¹⁰

Another limitation of this study is that we combined the results of a prospective cohort study nested within the HCRN's Core Data Project with those of our previously published retrospective cohort study.⁸ This decision was made in order to capture every ETV+CPC ever done at all of the 8 participating centers as well as to ensure inclusion of an unbiased sample of formally untrained procedures, including those done before a specific surgeon was trained at a later date. Another limitation is the subgroup analysis. Although this study represents the largest multicenter (predominantly prospective) study of ETV+CPC to our knowledge, we had the statistical power to conduct the univariable and multivariable analysis but not the subgroup analyses. Therefore, the reported subpopulations of potential benefit and failure for ETV+CPC should only be considered as hypothesis generating and require further validation.

Conclusions

This large, multicenter (predominantly prospective), North American cohort study demonstrated that young age and certain etiologies were independent predictors of ETV+CPC failure in the infant hydrocephalus population. Subpopulations combining specific age categories and etiologies were identified as potential targets that may preferentially derive benefit from ETV+CPC. These included most infants with myelomeningocele, those > 1 month corrected age with aqueductal stenosis, and those > 6 months corrected age with the post-IVH secondary to prematurity etiology. Although formal ETV+CPC training was associated with technical changes of practice, an increased degree of CPC, and changes in ETV+CPC failure management, this formal training was not found to be associated with improved ETV+CPC success.

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Appendix: HCRN Members

The HCRN currently consists of the following clinical centers and investigators: Primary Children's Hospital, University of Utah (J Kestle); Children's Hospital of Alabama, University of Alabama at Birmingham (C Rozzelle); Hospital for Sick Children, University of Toronto (J Drake, A Kulkarni); Texas Children's Hospital, Baylor College of Medicine (W Whitehead); Seattle Children's Hospital, University of Washington (S Browd, T Simon, J Hauptman); Children's Hospital of Pittsburgh, University of Pittsburgh (I Pollack); 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 (M Tamber, P McDonald); Alberta Children's Hospital, University of Calgary (J Riva-Cambrin); The Johns Hopkins Hospital (E Jackson); Children's Hospital of Los Angeles (M Krieger); Children's Hospital Colorado (T Hankinson); Nationwide Children's Hospital (J Pindrik); HCRN DCC, Department of Pediatrics, University of Utah (R Holubkov).

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Author Contributions

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

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