JNS PEDIATRICS

LITERATURE REVIEW

J Neurosurg Pediatr 31:423–432, 2023

Endoscopic third ventriculostomy for shunt malfunction in the pediatric population: a systematic review, meta-analysis, and meta-regression analysis

Keng Siang Lee, MBChB, MRes,[1–4] Aswin Chari, BMBCh,[1,2,5] Conor S. Gillespie, MBChB, MPhil,[6] Justyna O. Ekert, PhD,[1,2] Seyed Ehsan Saffari, PhD,[7,8] Greg James, MBBS, PhD,[1,2] and Kristian Aquilina, MD[1,2]

[1]Department of Neurosurgery, Great Ormond Street Hospital for Children, London, United Kingdom; [2]Developmental Neurosciences, Great Ormond Street Institute of Child Health, University College London, London, United Kingdom; [3]Department of Neurosurgery, King's College Hospital, London, United Kingdom; [4]Department of Basic and Clinical Neurosciences, Maurice Wohl Clinical Neuroscience Institute, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom; [5]Department of Neurosurgery, National Hospital for Neurology and Neurosurgery, London, United Kingdom; [6]Department of Clinical Neurosciences, University of Cambridge, Cambridge, United Kingdom; [7]Health Services and Systems Research, Duke–NUS Medical School, National University of Singapore, Singapore, Singapore; and [8]National Neuroscience Institute, Singapore, Singapore

OBJECTIVE Despite growing published evidence of the merits of endoscopic third ventriculostomy (ETV) instead of shunt revision at the time of shunt malfunction (secondary ETV), concerns about its efficacy and complications remain and ETV is still not used widely in this context. This study aimed to carry out a comprehensive meta-analysis and reports on the success and safety of secondary ETV in the pediatric age group.

METHODS In accordance with the PRISMA guidelines, systematic searches of Medline, Embase, and Cochrane Central were undertaken from database inception to September 7, 2022. ETV success was defined as the lack of need for a shunt and was the primary outcome measure. Secondary outcome measures were the rates of complications and mortality. A random-effects model was used. Summary-level meta-regression was performed to identify predictors for success in accordance with the ETV Success Score (ETVSS).

RESULTS Sixteen studies reporting on 584 patients who underwent secondary ETV for shunt malfunction were included in the meta-analysis. The overall pooled mean (95% CI) age was 6.1 (3–9) years, and 57.0% of patients were male. The pooled prevalence rates of the hydrocephalus etiologies were as follows: aqueduct stenosis (39.3%); myelomeningocele (27.6%); postinfectious (17.1%); posthemorrhagic (13.0%); neoplasm (13.0%); and malformation (11.3%). The overall pooled success rates of ETV for shunt malfunction at 3 months, 6 months, and 12 months were 65.69% (95% CI 52%–77%, prediction interval 47%–81%, $I^2 = 0$, $p = 0.775$); 63.25% (95% CI 54%–72%, prediction interval 38%–83%, $I^2 = 65$, $p < 0.001$); and 53.37% (95% CI 24%–81%, prediction interval 1%–99%, $I^2 = 47$, $p = 0.154$). The overall pooled prevalence of intraoperative bleeding was 4.96% (95% CI 0%–64%, prediction interval 0%–99%, $I^2 = 85$, $p < 0.001$). The overall rates of complications were low, with new neurological deficit (transient or permanent) having the highest rate at 1.61% (95% CI 0.68%–3.72%, prediction interval 0.67%–3.78%, $I^2 = 0$, $p > 0.999$). On meta-regression, age ($p = 0.138$), proportion of patients with postinfectious hydrocephalus ($p = 0.8736$), and number of shunt revisions ($p = 0.1775$) were not statistically significant predictors of secondary ETV success at 6 months.

CONCLUSIONS This meta-analysis demonstrates that secondary ETV after shunt malfunction in pediatric patients is a feasible option with acceptable success rates and low complication rates.

Clinical trial registration no.: CRD42022359573 (PROSPERO)

https://thejns.org/doi/abs/10.3171/2023.1.PEDS22427

KEYWORDS neuroendoscopy; neurosurgery; secondary endoscopic third ventriculostomy; hydrocephalus; shunt failure; malfunction

ABBREVIATIONS CSF = cerebrospinal fluid; ETV = endoscopic third ventriculostomy; ETVSS = ETV Success Score; EVD = external ventricular drain; GLMM = generalized linear mixed model; JBI = Joanna Briggs Institute.

SUBMITTED September 25, 2022. **ACCEPTED** January 17, 2023.
INCLUDE WHEN CITING Published online February 10, 2023; DOI: 10.3171/2023.1.PEDS22427.

Cerebrospinal fluid (CSF) shunting remains the mainstay treatment for patients with communicating and obstructive forms of hydrocephalus.[1–3] However, despite notable advancements in shunt technology, only meager improvements in the rates of malfunction and shunt-related complications have been realized.[4] A third of implanted shunts malfunction in the 1st year and approximately 80% of patients require a shunt revision in the next decade.[5]

Endoscopic third ventriculostomy (ETV) serves as a potential and attractive alternative to CSF shunting for hydrocephalus due to the lack of implanted hardware.[6–8] The effectiveness of primary ETV in obstructive hydrocephalus has been documented to lead to substantial rates of shunt independence.[6–8] Previous studies of ETV have focused on its role as an initial treatment for hydrocephalus. However, there may be a role for ETV in the context of shunt malfunction (secondary ETV) in preference to shunt revision.

According to the ETV Success Score (ETVSS), patient age, hydrocephalus etiology, and previous shunting are the most important factors influencing ETV effectiveness.[9,10] Previous shunting purportedly reduces the likelihood of ETV success by approximately 10%.[9,10] As a result, many children who previously underwent shunting were considered eligible candidates for ETV but may not have been offered the procedure. However, large series on both pediatric and adult patients have shown similar rates of shunt independence between primary and secondary ETV.[11,12]

Consequently, this present study aimed to review the clinical and safety outcomes of ETV in children with a history of previous CSF shunt insertion through a systematic review and meta-analysis.

Methods

This review was conducted according to the PRISMA guidelines.[13] The protocol was registered with the international prospective PROSPERO registry of systematic reviews (registration no. CRD42022359573).

Outcomes

The primary outcome was ETV success, as defined as the absence of shunt surgery at a minimum 3-month follow-up. In most cases, the objective for secondary ETV is to render the patient shunt free. Hence, secondary ETV followed by temporary external ventricular drain (EVD) placement or further ETV would not be considered failed secondary ETV. Nonetheless, the use of temporary EVD after ETV was investigated.

Secondary outcomes that were considered complications after secondary ETV included any new neurological deficit, diabetes insipidus, hyponatremia, wound infection, intracranial fluid collection, CSF leak, pseudomeningocele, seizure, meningitis, sepsis, hemorrhage, and procedure-related mortality, as defined by the authors. Intraoperative bleeding outcomes defined as bleeding during procedure were also included.

Search Strategy

Three electronic databases—Ovid Medline, Ovid Embase, and Cochrane Central Register of Controlled Trials (CENTRAL)—were searched. Searches were performed in each electronic database from its inception until September 7, 2022. In addition to their synonyms and related terms, the concepts of "endoscopic third ventriculostomy" and "shunt failure" were used. Supplementary Table 1 presents the full search strategy used for each database.

Eligibility Criteria

Articles were selected for inclusion if they were a primary interventional or observational study that evaluated the effectiveness and safety of ETV after shunt malfunction, with follow-up of at least 3 months. Studies that had evaluated primary and secondary ETV but reported outcomes specific to secondary ETV were included. This review included studies on exclusively pediatric patients (age < 18 years).

The following studies were excluded: narrative and systematic reviews, editorials, commentaries, opinion papers, letters, education papers, conference abstracts, protocols, reports, theses, or book chapters because they were unlikely to contain sufficient detail about the effectiveness and safety of both treatments. Non-English articles were also excluded. Supplementary Table 2 provides the full list of inclusion and exclusion criteria.

Study Selection

Titles and abstracts were independently screened against the predefined eligibility criteria developed by two reviewers (K.S.L. and C.S.G.). Any disagreements were resolved through discussion between the reviewers or further adjudication by a third reviewer (K.A.). Agreement among the reviewers on study inclusion was evaluated with Cohen's kappa.[14]

Studies with small sample sizes were included on the basis of the recommendations of the Cochrane Statistical Methods Group to not exclude studies purely on the basis of sample size.[15] When multiple publications analyzing the same cohort over overlapping study periods were encountered, the publication that reported the largest patient data set with the relevant outcomes was used for evaluation.

The reference lists of the included studies were explored to identify any relevant studies that may have been inadvertently overlooked in our search strategy.[16]

Data Extraction

To ensure standardization and consistency, a pro forma was developed and piloted to extract data on the following variables: 1) study details, 2) study design, 3) country and data set, 4) selection criteria, 5) patient demographic characteristics, 6) treatment and control, 7) indication for treatment, and 8) results. K.S.L. and C.S.G. independently extracted the data to ensure reliability. Discrepancies or disagreements about extracted material were resolved by the senior reviewer (K.A.).

Risk of Bias Assessment

The risk of bias of the included studies was assessed using the Joanna Briggs Institute (JBI) checklist for case series.[17] The JBI checklist rated the quality of selection,

measurement, and comparability for all studies and gave a score of 10. K.S.L. and C.S.G. assessed the risk of bias of all included studies and discussed discrepancies until consensus was reached.

Statistical Analysis

Meta-analyses of the primary endpoints were performed via the random-effects model due to heterogeneity within and between individual studies, as well as sampling variabilities across studies.[18]

The overall pooled proportions of hydrocephalus etiology, as well as the rates of success and complications, of the included patients were computed using the generalized linear mixed model (GLMM) method with a random intercept logistic regression model via logit transformation.[18,19] Knapp-Hartung adjustments were used to reduce the chance of false-positive results and to control the estimated uncertainties of between-study heterogeneity. GLMM, instead of Freeman-Tukey double arcsine transformation, was employed because GLMM has been shown to provide the most accurate estimate for meta-analysis of single proportions in simulation studies.[18,19]

The I^2 statistic was employed to assess interstudy heterogeneity. I^2 provides an estimate of the percentage of variability in results across studies that is due to real differences and not due to chance. $I^2 \leq 30\%$, 30%–50%, 50%–75%, and $\geq 75\%$ indicated low, moderate, substantial, and considerable heterogeneity, respectively.[20] The p values for the I^2 statistic were derived from the chi-square distribution of Cochran's Q test. Prediction intervals were reported for all outcome measures. A prediction interval provides estimates of what the effect size might be for similar studies conducted in the future.

Missing mean ± SD values for the numerical variables were imputed as medians, ranges (minimum to maximum), and interquartile ranges by using the methods proposed by Hozo et al. and Wan et al.[21,22]

Summary-level meta-regression was performed using mixed-effect meta-analysis modeling with the GLMM method to identify predictors for secondary ETV success at 6 months. A maximum likelihood estimator was used to estimate heterogeneity. Predictors were patient age, hydrocephalus etiology, and previous shunting in accordance with ETVSS.[9,10]

The publication bias of the studies was assessed using funnel plots, where an asymmetrical distribution of studies was suggestive of bias.[23] The Egger's regression test was performed for quantitative analysis of funnel plot asymmetry.[24] The quality of evidence for each outcome was evaluated using the GRADE (Grading of Recommendations, Assessment, Development and Evaluations) framework.[25]

All statistical analyses were performed using R software version 4.2.1 (R Foundation for Statistical Computing), with the package meta.[26] In this study, $p < 0.05$ was considered statistically significant.

Results

Characteristics of Included Studies

The systematic search yielded 672 unique publications.

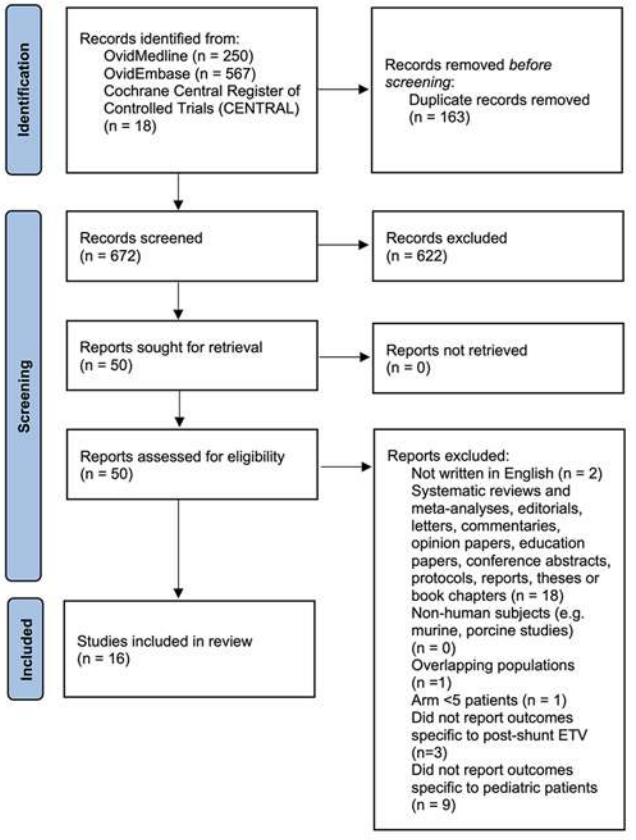

FIG. 1. PRISMA flow diagram of the studies that were included and excluded from the systematic review and meta-analysis. Data added to the PRISMA template [from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71]. Figure is available in color online only.

After screening of the titles and abstracts, the full texts of 50 publications were reviewed. Sixteen studies with 584 patients met the eligibility criteria for inclusion in our systematic review and meta-analysis (Fig. 1).[6,27–41] At screening of both the title and abstract, the reliability of study selection between reviewers was substantial (Cohen's κ 0.89 and 1.00, respectively).[14]

All 16 included studies were nonrandomized observational case series. Data were collected across 14 countries: China, India, Japan, Egypt, Iran, Saudi Arabia, Turkey, Brazil, Czech Republic, France, Italy, Netherlands, United States, and United Kingdom. Table 1 presents a summary of the included studies. In the evaluation of the risk of bias with the JBI checklist for case series, 7 studies attained a full score of 10, 3 studies attained a score of 9, 3 studies attained a score of 8, and 3 studies attained a score of 7 (see Supplementary Table 3 for full details).

Baseline Characteristics of Patients and Workflow

Patient sex was reported in 9 of 16 studies, for a total of 402 patients: 56.97% were male and 43.03% were female. The mean ± SD age was reported or imputable in 8 of 16 studies, for a total of 371 patients. The overall

TABLE 1. Summary of included studies

Authors & Year	Country	Study Design	Study Period	Total No. of Patients	Imputed Age (yrs)*	Male	Imputed Follow-Up (mos)*
Beems & Grotenhuis, 2002[27]	Netherlands	Case series	Through 2001	13	0.60 ± 0.44	NR	55.46 ± 32.92
Brichtova et al., 2013[28]	Czech Republic	Case series	2001–2011	42	9.5 ± NR	24 (57.14)	NR
Choudhary et al., 2020[29]	India	Case series	2010–2016	36	0.17–16†	24 (66.67)	NR
Cinalli et al., 1998[6]	France	Case series	1987–1993	30	8.7 ± NR	21 (70.00)	61.75 ± 58.09
Duru et al., 2018[30]	Turkey	Case series	2001–2016	8	NR	NR	NR
Elgamal, 2010[31]	Saudi Arabia	Case series	NR	7	NR	1 (14.29)	NR
Furtado et al., 2020[32]	Brazil	Case series	1996–2016	43	NR	20 (46.51)	NR
Heshmati et al., 2019[33]	Iran	Case series	2008–2014	33	5.70 ± 4.06	NR	18.05 ± 10.22
Kenawy et al., 2022[34]	Egypt	Case series	2017–2020	18	11.17 ± 5.16	11 (61.11)	NR
Marton et al., 2010[35]	Italy	Case series	1995–2008	22	7.09 ± 4.41	NR	66.75 ± 35.50
Rocque et al., 2022[36]	Canada, USA	Multicenter case series; HCRN registry	2008–2019	203	5.10 ± 6.81	115 (56.65)	NR
Shaikh et al., 2019[37]	India	Case series	2004–2018	36	9.25 ± 5.73	NR	46.26 ± 52.93
Shimizu et al., 2012[38]	Japan, USA	Multicenter case series; Cleveland Clinic, National Hospital Organization, Okayama Medical Center	2000–2009	9	9.36 ± 5.87	5 (55.56)	NR
Stovell et al., 2016[39]	UK	Case series	1998–2006	33	NR	NR	99.20 ± 61.64
Tamburrini et al., 2007[40]	Italy	Case series	2001–2007	14	2.65 ± NR	8 (57.14)	79.71 ± 9.30
Zhao et al., 2016[41]	China	Case series	2005–2014	37	1.83 ± 0.75	NR	NR

HCRN = Hydrocephalus Clinical Research Network; NR = not reported.
Values are shown as number, number (%), or mean ± SD.
* To pool the means of the numerical variables, we computed missing mean ± SD values from the medians, ranges (minimum to maximum), and interquartile ranges by using the methods proposed by Hozo et al.[21] and Wan et al.[22]
† The range is reported.

pooled mean age across these studies was 6.08 years (95% CI 3–9, $I^2 = 98\%$, $p < 0.001$).

The pooled prevalence of hydrocephalus etiologies was as follows: aqueduct stenosis (39.33%, 95% CI 19%–64%, $I^2 = 73$, $p < 0.001$); myelomeningocele (27.58%, 95% CI 26%–28%, $I^2 = 0$, $p = 0.433$); postinfectious (17.12%, 95% CI 11%–26%, $I^2 = 17$, $p = 0.298$); posthemorrhagic (12.98%, 95% CI 6%–26%, $I^2 = 59$, $p = 0.007$); neoplasm (12.97%, 95% CI 6%–25%, $I^2 = 48$, $p = 0.073$); and malformation (Dandy-Walker syndrome and Chiari malformation) (11.32%, 95% CI 5%–25%, $I^2 = 3$, $p = 0.376$). The pooled prevalence rates of the baseline characteristics are summarized in Table 2. There were overlapping etiologies within the included patients and hence the etiologies were not exclusive.

In total, 28.91% (95% CI 18%–42%, $I^2 = 71$, $p < 0.001$) of patients presented with shunt infection. The pooled mean number of shunt revisions before ETV was 2.24 (95% CI 0.28–18.24, $I^2 = 95$, $p < 0.001$). The mean ± SD interval between last shunt placement to ETV was reported or imputable in 3 studies for a total of 122 patients. The pooled time interval between last shunt placement and ETV was 46.83 months (95% CI 1–93, $I^2 = 96$, $p < 0.001$).

Primary Outcome

Success Rates

The mean ± SD follow-up duration was reported in 7 studies. The pooled follow-up duration was 60.37 months (95% CI 36–84, $I^2 = 98$, $p < 0.001$). The overall pooled success rate of ETV for shunt malfunction at last follow-up was 58.57% (95% CI 44%–72%, prediction interval 20%–89%, $I^2 = 83$, $p < 0.001$). The overall pooled success rates of ETV for shunt malfunction at 3 months, 6 months, and 12 months were 65.69% (95% CI 52%–77%, prediction interval 47%–81%, $I^2 = 0$, $p = 0.775$), 63.25% (95% CI 54%–72%, prediction interval 38%–83%, $I^2 = 65$, $p < 0.001$), and 53.37% (95% CI 24%–81%, prediction interval 1%–99%, $I^2 = 47$. $p = 0.154$) (Fig. 2). On meta-regression, age ($p = 0.138$), proportion of patients with postinfectious hydrocephalus ($p = 0.8736$), and number of shunt revisions ($p = 0.1775$) were not statistically significant predictors of secondary ETV success at 6 months.

The success rates according to hydrocephalus etiology were highest for aqueduct stenosis, followed by posthemorrhagic hydrocephalus, myelomeningocele, and postinfectious hydrocephalus. The results of the analysis of the success rates for neoplasm and malformation were omitted because only 2 studies reported these characteristics for a few patients. Table 3 provides the pooled outcomes.

Temporary EVD use during the ETV procedure was reported across 6 studies, including 303 patients. The overall pooled rate of postoperative EVD use was 33.46% (95% CI 5%–84%, prediction interval 0%–99%, $I^2 = 84$, p

TABLE 2. Pooled baseline characteristics of the included patients

Characteristic	No. of Studies Reporting Variable	Total Sample Analyzed	Pooled Summary Estimate (95% CI)	I^2 (%)	p Value of I^2*
Male sex	9	402	56.97 (51.20–62.54)	12.0	0.3344
Mean age, yrs	8	371	6.08 (2.96–9.19)	97.9	<0.0001
Workflow					
Shunt infection	11	480	28.91 (18.84–41.61)	71.1	<0.0001
Time from last shunt placement to ETV, mos	4	122	46.83 (1.03–92.62)	96.1	<0.0001
Mean no. of shunt revisions before ETV	3	240	2.24 (0.28–18.24)	94.8	<0.0001
Mean follow-up, mos	7	181	60.37 (36.41–84.33)	98.7	<0.001
Hydrocephalus etiology					
Aqueduct stenosis	11	479	39.33 (18.98–64.20)	73.2	<0.0001
Myelomeningocele	6	337	27.58 (26.52–28.67)	0.0	0.4333
Postinfectious	8	231	17.12 (10.91–25.84)	16.7	0.2982
Posthemorrhagic	11	479	12.98 (5.93–26.09)	58.5	0.0074
Neoplasm	7	185	12.97 (6.14–25.35)	48.0	0.0732
Malformation†	4	106	11.32 (4.59–25.30)	3.4	0.3755

* Determined with the chi-square test.
† Includes Dandy-Walker syndrome and multiloculated hydrocephalus.

< 0.001). No studies reported data on return to the operating room for EVD insertion after ETV.

Secondary Outcomes

Complication Rates

Intraoperative bleeding was reported in 4 studies. The overall pooled prevalence of intraoperative bleeding was 4.96% (95% CI 0%–64%, prediction interval 0%–100%, $I^2 = 85$, $p < 0.001$). Only Rocque et al. formally graded the level of intraoperative bleeding.[36] Moderate intraoperative bleeding was defined as a totally obstructed view that cleared within 2–3 minutes, whereas severe intraoperative bleeding required more than 5 minutes to return to clear working conditions. In our meta-analysis, severe intraoperative bleed also included the need to abort the procedure. The rates of moderate and severe bleeding were 1.45% (95% CI 0%–80%, prediction interval 0%–99%, $I^2 = 66$, $p = 0.0887$) and 1.38% (95% CI 0%–7%, prediction interval 0%–11%, $I^2 = 0$, $p = 0.762$).

The overall rates of complications were acceptable. A new neurological deficit (transient or permanent) was present in 1.61% of patients (95% CI 0.68%–3.72%, prediction interval 0.67%–3.78%, $I^2 = 0$, $p > 0.999$). CSF leak was reported in 11 studies for 454 patients. The overall pooled prevalence of CSF leak was 0.55% (95% CI 0.02%–15.66%, prediction interval 0.00%–84.36%, $I^2 = 0$, $p = 0.956$).

Wound infection, diabetes insipidus, intracranial fluid collection, hyponatremia, sepsis, meningitis, seizures, and pseudomeningocele were reported in 10 studies that included 436 patients. The pooled prevalence rates of the abovementioned complications were as follows: wound infection (0.46%, 95% CI 0.09%–2.24%, prediction interval 0.09%–2.31%, $I^2 = 0$, $p > 0.999$); intracranial fluid collection (0.51%, 95% CI 0.02%–11.62%, prediction interval 0.01%–15.20%, $I^2 = 0$, $p > 0.999$); hyponatremia (0.53%, 95% CI 0.03%–9.94%, prediction interval 0.00%–66.84%, $I^2 = 64$, $p = 0.003$); sepsis (0.51%, 95% CI 0.02%–11.62%, prediction interval 0.01%–15.20%, $I^2 = 0$, $p > 0.999$); meningitis (0.51%, 95% CI 0.02%–11.62%, prediction interval 0.01%–15.20%, $I^2 = 0$, $p > 0.999$); seizures (0.11%, 95% CI 0.00%–73.14%, prediction interval 0.00%–92.33%, $I^2 = 0$, $p > 0.999$); and pseudomeningocele (0.60%, 95% CI 0.03%–9.58%, prediction interval 0.01%–25.98%, $I^2 = 0$, $p > 0.999$). Due to the extreme 95% CI values for the pooled prevalence of diabetes insipidus, this characteristic was omitted because we considered this estimate unreliable.

The overall rates of hemorrhage were reported in 10 studies for 436 patients. The rates of intraventricular hemorrhage, intracerebral hemorrhage, and extradural hematoma were 0.92% (95% CI 0%–3%, prediction interval 0%–3%, $I^2 = 0$, $p > 0.999$), 0.23% (95% CI 0%–2%, prediction interval 0%–2%, $I^2 = 0$, $p > 0.999$), and 0.16% (95% CI 0%–16%, prediction interval 0%–25%, $I^2 = 0$, $p > 0.999$), respectively.

Procedure-related mortality was reported in 11 studies and occurred in 2 of 454 patients in these studies. The overall pooled procedure-related mortality rate was 0.03% (95% CI 0%–89%, prediction interval 0%–98%, $I^2 = 0$, $p > 0.999$) (Supplementary Fig. 1). Due to the extreme 95% CI, we advise that this estimate is not reliable. The crude estimate of procedure-related mortality was 0.44% (95% CI 0.05%–1.58%), determined with the Clopper-Pearson (exact) binomial method.

As shown in Supplementary Fig. 1, procedure-related mortality was observed in only 1 of 11 studies. Accordingly, procedure-related mortality ranged from as low as 0% to as high as 4.76%, across 11 studies. The forest plots for all other reported outcomes from each study can be found in Supplementary Figs. 2–15.

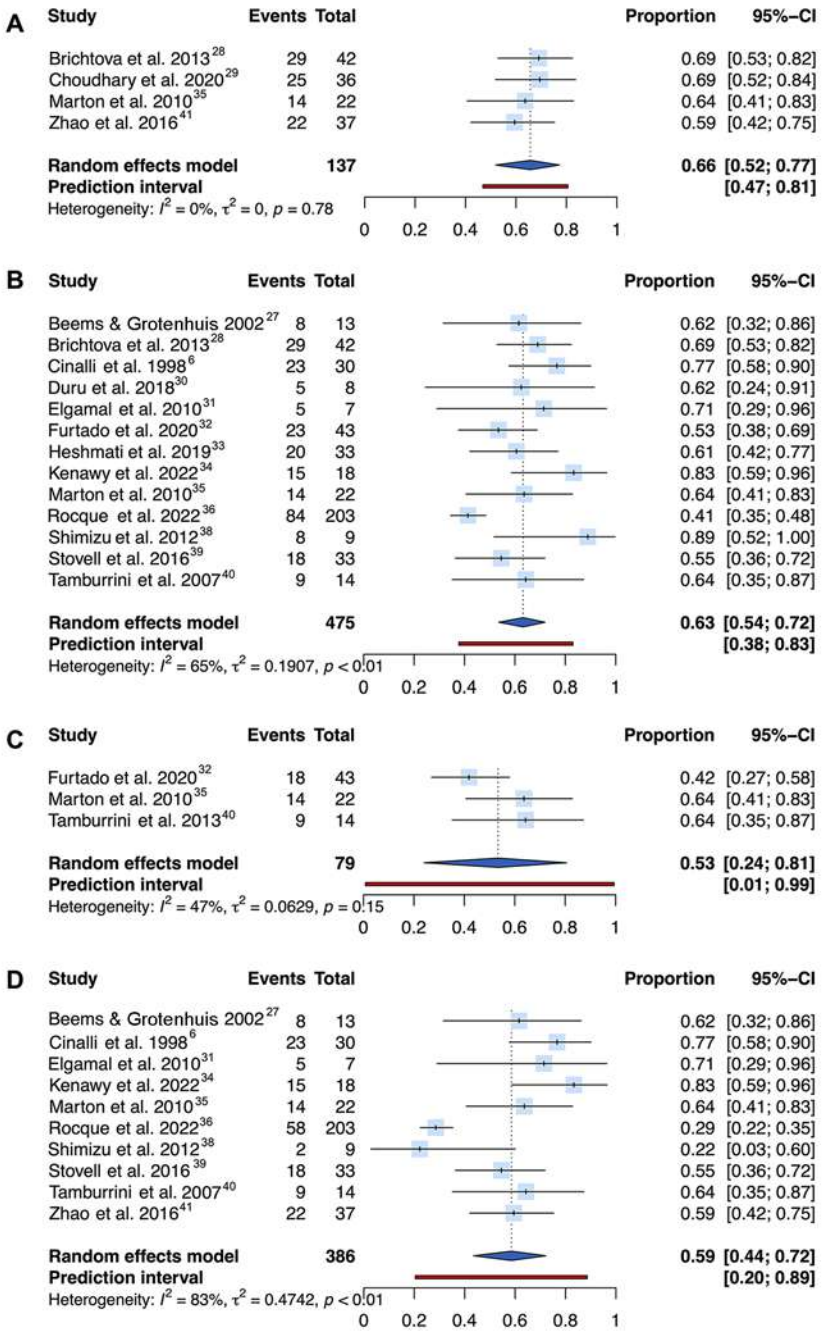

FIG. 2. Forest plots of good success rates determined with random-effects models at 3 months (**A**), 6 months (**B**), 12 months (**C**), and last follow-up (**D**). Figure is available in color online only.

Discussion

Summary of Findings

This is the largest study to systematically assess the role of ETV in children with a history of previous treatment with CSF shunt insertion, in terms of success and complication rates, by using a systematic review and meta-analysis.[42,43] This study demonstrated relatively good overall pooled rates of success at 3, 6, and 12 months of follow-up, as well as low rates of complications, suggesting that secondary ETV is an effective and safe option for the pediatric population presenting with shunt malfunction.

Comparison With Findings in the Literature

Primary ETV is purportedly effective, with reported rates of shunt independency ranging from 60% to 70%.[7,44] This meta-analysis demonstrates comparable success rates for secondary ETV at various time points at 3, 6, 12, and 60 months (55%–60%). These results are also corrobo-

TABLE 3. Pooled outcomes of included patients

Outcome	No. of Studies Reporting Variable	No. of Patients Analyzed	Pooled Summary Estimate (95% CI)*	I^2 (%)	p Value of I^2†	Prediction Interval	Quality of Evidence‡
Overall success rate							
3 mos	4	137	65.69 (51.92–77.25)	0.0	0.775	46.89–80.60	Low
6 mos	13	475	63.25 (53.62–71.93)	64.7	<0.001	37.78–82.99	Low
12 mos	3	79	53.37 (24.03–80.54)	46.6	0.154	0.80–99.39	Low
Last follow-up	10	386	58.57 (43.53–72.16)	83.3	<0.001	20.46–88.60	Low
Success rate stratified by hydrocephalus etiology							
Aqueduct stenosis	4	54	74.07 (51.54–88.47)	0.0	0.640	0.42.89–0.91.57	Low
Posthemorrhagic	4	21	61.90 (28.00–87.16)	0.0	0.947	19.03–91.83	Low
Myelomeningocele	3	51	54.90 (26.62–80.34)	0.0	0.826	3.30–97.75	Low
Postinfectious	3	19	52.63 (13.34–88.92)	0.0	0.994	0.32–99.74	Low
Complications							
Temporary EVD use during ETV procedure	6	303	33.46 (4.68–83.73)	84.0	<0.001	0.10–99.62	Low
Intraop bleeding	4	289	4.96 (0.15–64.14)	84.8	<0.001	0.00–99.77	Low
Moderate bleeding	4	289	1.45 (0.01–79.88)	65.5	0.089	0.00–98.64	Low
Severe bleeding	4	289	1.38 (0.28–6.51)	0.0	0.762	0.16–10.91	Low
New neurological deficit	10	436	1.61 (0.68–3.72)	0.0	>0.999	0.67–3.78	Low
Oculomotor paralysis	8	248	1.11 (0.12–9.30)	0.0	>0.999	0.10–11.72	Low
CSF leak	11	454	0.55 (0.02–15.66)	0.0	0.956	0.00–84.36	Low
Wound infection	10	436	0.46 (0.09–2.24)	0.0	>0.999	0.09–2.31	Low
Intracranial fluid collection	10	436	0.51 (0.02–11.62)	0.0	>0.999	0.01–15.20	Low
Hyponatremia	10	436	0.53 (0.03–9.94)	63.7	0.003	0.00–66.84	Low
Sepsis	10	436	0.51 (0.02–11.62)	0.0	>0.999	0.01–15.20	Low
Meningitis	10	436	0.51 (0.02–11.62)	0.0	>0.999	0.01–15.20	Low
Seizure	10	436	0.11 (0.00–73.14)	0.0	>0.999	0.00–92.33	Low
Pseudomeningocele	10	436	0.60 (0.03–9.58)	0.0	>0.999	0.01–25.98	Low
IVH	10	436	0.92 (0.30–2.80)	0.0	>0.999	0.29–2.86	Low
ICH	10	436	0.23 (0.02–2.17)	0.0	>0.999	0.02–2.26	Low
EDH	10	436	0.16 (0.00–15.60)	0.0	>0.999	0.00–25.39	Low
Procedure-related mortality*	11	454	0.03 (0.00–88.91)	0.0	>0.999	0.00–98.21	Low

EDH = extradural hematoma; ICH = intracerebral hemorrhage; IVH = intraventricular hemorrhage.

* When the pooled proportions (GLMM method) provided 95% CI values of 0 to 1 or nearly 1, then we considered that estimate as unreliable.

† Determined with the chi-square test.

‡ According to the GRADE framework.

rated by studies with mixed adult and pediatric patients who had undergone previous shunt implantation (52%–90%).[45–49] Notably, in our study, the pooled rates of success at last follow-up (mean 5 years) were higher than at 12 months (58.57% vs 53.37%). A likely explanation is related to the fact that 10 studies with 386 patients reported success rates at last follow-up, whereas only 3 studies with a total of 79 patients reported success rates at 12 months, with the former hence giving a more reliable point estimate. Kulkarni et al. showed that primary ETV was associated with a greater early-failure rate, but this rate decreases with time to a level lower than that of the failure rate associated with shunt placement.[7,9,10] This is consistent with our pooled success rates for secondary ETV at the subsequent time interval. Nonetheless, ETV failure should not be overlooked during clinical follow-up of these patients in order to mitigate any late, sudden deterioration that could be catastrophic.[42] Although not considered to represent failed secondary ETV, post-ETV EVD is an important consideration because it requires another visit to the operating room and represents an aspect of morbidity. However, among the primary studies, no such information was obtained and hence could not be synthesized.

The etiology of hydrocephalus is a crucial factor considered to influence ETV success.[7,9,10] Our findings demonstrated that secondary ETV was successful in 75% of children with aqueduct stenosis. This is corroborated by previous studies for primary ETV.[50–52] Furlanetti et al. reported a similar success rate of 88% in primary ETV.[50] Conversely, the lowest success rate, as expected, was recorded

in patients with postinfectious hydrocephalus (52%).[7,9,10] Differences in etiology of hydrocephalus may account for the differences in the reported success rates of secondary ETV. In a recent study from North America, which estimated a 6-month success rate of only 40% for secondary ETV, the most prevalent cause of hydrocephalus in the cohort was posthemorrhagic in 27% of patients,[36] whereas in this meta-analysis, which also included patients from Europe, South America, Asia, and Africa, posthemorrhagic hydrocephalus only accounted for 13% of patients, with aqueduct stenosis being far more common at almost 40%.

Although beneficial, we recognize that, based on the information from the included studies, our current meta-analysis could not externally validate the ETVSS model and its predictive accuracy of ETV success at 6 months.[9,10] A possible relationship with more granular detail may be uncovered in the future. Validation could be achieved by establishing a prospective registry with data collected from multiple international centers, which could inform future meta-analyses with individual participant–level data from real-world settings. Nonetheless, the strength of this current meta-analysis lies in its ability to perform meta-regression analyses in order to identify predictors such as patient age, hydrocephalus etiology, and previous shunting in accordance with ETVSS.[9,10]

The rates of complications from ETV have been shown to be greater in patients with a history of previous ventriculoperitoneal shunt implantation compared with primary ETV, with death as a possible consequence of ETV failure,[7,52,53] although our pooled analysis showed that mortality is low (0.03%).[7,52,53] This meta-analysis observed an acceptable rate of complications, with the most common being transient or permanent neurological deficit (1.61%), pseudomeningocele (0.60%), and CSF leak (0.55%). However, in this study, the rate of intraoperative bleeding was 5%. The rates of severe hemorrhage and basilar artery rupture—a feared intraoperative complication of ETV—were reported in 1% of cases. This is not insignificant. However, multivariable analyses by Rocque et al. found that time to shunt surgery (failure) after secondary ETV was not affected by the presence of intraoperative hemorrhage, although they found that a clear surgical view of the basilar artery in the prepontine cistern was associated with greater likelihood of ETV success.[36] Secondary ETV is often performed in the presence of relatively small ventricles, and the importance of surgical experience cannot be overstated.

Clinical Implications

Because this meta-analysis did not directly compare secondary ETV as an alternative treatment to standard shunt revision in children presenting with shunt malfunction, we can at best only conclude that secondary ETV is a safe and relatively effective option. A significant proportion of children reviewed in this study underwent secondary ETV for shunt infection.[6,28,30–38,41] This is attractive because ETV allows for removal of implanted hardware. However, our meta-analysis suggests that secondary ETV may be equally suitable for patients with other causes of shunt malfunction.

There was distinguishable variation with respect to the overall success and complication rates for secondary ETV among the case series included in our review. This could be attributed to heterogeneity in the way the incidents were recorded as complications. However, this may also be related to true differences in the complication rates between centers and individual neurosurgeons.[42] With acknowledgment of the anatomical differences between shunt-naive and shunt-dependent patients, secondary ETV is more technically demanding than primary and is associated with a higher intraoperative complication rate. It is critical to define an optimal trajectory through what is usually a relatively small ventricular system. The use of neuronavigation is advised.

Limitations

The limitations of our meta-analysis stem from the retrospective and observational nature of included case series, with notable heterogeneity among them. Conclusions drawn from this meta-analysis may have been biased by residual confounders. Confounders not accounted for in this study include surgeon experience. This may have introduced selection and performance bias, potentially steering our conclusions in either direction. There was no standard time frame, with different lengths of clinical follow-up in each study. In addition, several outcomes reported in this study had large encompassing 95% CI values, which may be explained by the modest sample size and large heterogeneity among studies. As such, a few outcomes were omitted to avoid misinterpretation because the estimates were unlikely to be reliable. Notably, the prediction intervals suggested considerable between-study variation in outcomes. This limits our ability for clinicians to quote figures confidently.[18] This meta-analysis included patients who had undergone both ETV and choroid plexus cauterization. However, subgroup analyses of the success rates for this specific cohort of patients could not be performed due to the lack of granular data from primary studies, which could be disaggregated specifically for these patients. The main value of our meta-analysis was the avoidance of undue emphasis on individual studies, thus yielding more reliable point estimates. Our meta-analysis included a diverse range of patients from all over the world, enhancing its external validity and facilitating our improved understanding of the appropriate therapeutic strategies.

Conclusions

This meta-analysis demonstrates that secondary ETV in pediatric patients is a feasible option, with relatively good success rates and low complication rates, and worth considering at shunt malfunction.

Acknowledgments

A special thank you to Kenneth Kek Wee Lee (Papa), Lena Lim (Mama), and Chio Tee Koh (Ahma) back home for their unwavering support, without which I (K.S.L.) would not be able to achieve my educational goals. Love truly overcomes all obstacles (different time zones and distance).

Dr. Chari is supported by a Great Ormond Street Hospital (GOSH) Children's Charity Surgeon Scientist Fellowship (no.

VS0319) and the GOSH–National Institute of Health Research Biomedical Research Centre. The sponsor had no role in the design or conduct of this research.

References

1. Isaacs AM, Ball CG, Sader N, et al. Reducing the risks of proximal and distal shunt failure in adult hydrocephalus: a shunt outcomes quality improvement study. *J Neurosurg*. 2021;136(3):877-886.
2. Drake JM, Kestle JR, Milner R, et al. Randomized trial of cerebrospinal fluid shunt valve design in pediatric hydrocephalus. *Neurosurgery*. 1998;43(2):294-305.
3. Drake JM, Kestle J. Determining the best cerebrospinal fluid shunt valve design: the pediatric valve design trial. *Neurosurgery*. 1996;38(3):604-607.
4. Di Rocco C, Marchese E, Velardi F. A survey of the first complication of newly implanted CSF shunt devices for the treatment of nontumoral hydrocephalus. Cooperative survey of the 1991-1992 Education Committee of the ISPN. *Childs Nerv Syst*. 1994;10(5):321-327.
5. Prusseit J, Simon M, von der Brelie C, et al. Epidemiology, prevention and management of ventriculoperitoneal shunt infections in children. *Pediatr Neurosurg*. 2009;45(5):325-336.
6. Cinalli G, Salazar C, Mallucci C, Yada JZ, Zerah M, Sainte-Rose C. The role of endoscopic third ventriculostomy in the management of shunt malfunction. *Neurosurgery*. 1998;43(6):1323-1329.
7. Kulkarni AV, Drake JM, Mallucci CL, Sgouros S, Roth J, Constantini S. Endoscopic third ventriculostomy in the treatment of childhood hydrocephalus. *J Pediatr*. 2009;155(2):254-9.e1.
8. Kulkarni AV, Hui S, Shams I, Donnelly R. Quality of life in obstructive hydrocephalus: endoscopic third ventriculostomy compared to cerebrospinal fluid shunt. *Childs Nerv Syst*. 2010;26(1):75-79.
9. Kulkarni AV, Drake JM, Kestle JR, Mallucci CL, Sgouros S, Constantini S. Predicting who will benefit from endoscopic third ventriculostomy compared with shunt insertion in childhood hydrocephalus using the ETV Success Score. *J Neurosurg Pediatr*. 2010;6(4):310-315.
10. Kulkarni AV, Riva-Cambrin J, Browd SR. Use of the ETV Success Score to explain the variation in reported endoscopic third ventriculostomy success rates among published case series of childhood hydrocephalus. *J Neurosurg Pediatr*. 2011;7(2):143-146.
11. Boschert J, Hellwig D, Krauss JK. Endoscopic third ventriculostomy for shunt dysfunction in occlusive hydrocephalus: long-term follow up and review. *J Neurosurg*. 2003;98(5):1032-1039.
12. Breimer GE, Dammers R, Woerdeman PA, et al. Endoscopic third ventriculostomy and repeat endoscopic third ventriculostomy in pediatric patients: the Dutch experience. *J Neurosurg Pediatr*. 2017;20(4):314-323.
13. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372(71):n71.
14. Cohen J. A coefficient of agreement for nominal scales. *Educ Psychol Meas*. 1960;20(1):37-47.
15. Grainge M. Excluding small studies from a systematic review or meta-analysis. Presented at: CSG Annual Meeting 2015; March 12-18, 2015; Dresden, Germany. Accessed January 20, 2023. https://skin.cochrane.org/sites/skin.cochrane.org/files/public/uploads/CSG-COUSIN_March%202015_M%20Grainge.pdf
16. Greenhalgh T, Peacock R. Effectiveness and efficiency of search methods in systematic reviews of complex evidence: audit of primary sources. *BMJ*. 2005;331(7524):1064-1065.
17. Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. *J Evid Based Med*. 2015;8(1):2-10.
18. Lee KS, Zhang JJY, Nga VDW, et al. Tenets for the proper conduct and use of meta-analyses: a practical guide for neurosurgeons. *World Neurosurg*. 2022;161:291-302.e1.
19. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. *Res Synth Methods*. 2019;10(3):476-483.
20. Higgins JPT, Thomas J, Chandler J, et al. *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.3. Cochrane; 2022.
21. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5(1):13.
22. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14(1):135.
23. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ*. 2011;343:d4002.
24. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
25. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926.
26. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4):153-160.
27. Beems T, Grotenhuis JA. Is the success rate of endoscopic third ventriculostomy age-dependent? An analysis of the results of endoscopic third ventriculostomy in young children. *Childs Nerv Syst*. 2002;18(11):605-608.
28. Brichtova E, Chlachula M, Hrbac T, Lipina R. Endoscopic third ventriculostomy in previously shunted children. *Minim Invasive Surg*. 2013;2013:584567.
29. Choudhary A, Sobti S, Zambre S, Bhaskar S. Endoscopic third ventriculostomy in failed ventriculoperitoneal shunt in pediatric population. *Asian J Neurosurg*. 2020;15(4):937-940.
30. Duru S, Peiro JL, Oria M, et al. Successful endoscopic third ventriculostomy in children depends on age and etiology of hydrocephalus: outcome analysis in 51 pediatric patients. *Childs Nerv Syst*. 2018;34(8):1521-1528.
31. Elgamal EA. Continuous monitoring of intracranial pressure after endoscopic third ventriculostomy in the management of CSF shunt failure. *Minim Invasive Neurosurg*. 2010;53(2):49-54.
32. Furtado LMF, da Costa Val Filho JA, Holliday JB, et al. Endoscopic third ventriculostomy in patients with myelomeningocele after shunt failure. *Childs Nerv Syst*. 2020;36(12):3047-3052.
33. Heshmati B, Habibi Z, Golpayegani M, Salari F, Anbarlouei M, Nejat F. Endoscopic third ventriculostomy in children with failed ventriculoperitoneal shunt. *Asian J Neurosurg*. 2019;14(2):399-402.
34. Kenawy K, Naser K, Kasim AK. Replacement of complicated VP shunts with endoscopic third ventriculostomy, local experience and outcome. *Egypt J Hosp Med*. 2022;87(1):1653-1657.
35. Marton E, Feletti A, Basaldella L, Longatti P. Endoscopic third ventriculostomy in previously shunted children: a retrospective study. *Childs Nerv Syst*. 2010;26(7):937-943.
36. Rocque BG, Jensen H, Reeder RW, et al. Endoscopic third ventriculostomy in previously shunt-treated patients. *J Neurosurg Pediatr*. 2022;30(4):428-436.

37. Shaikh S, Deopujari CE, Karmarkar V, Muley K, Mohanty C. Role of secondary endoscopic third ventriculostomy in children: review of an institutional experience. *Pediatr Neurosurg*. 2019;54(3):188-195.
38. Shimizu T, Luciano MG, Fukuhara T. Role of endoscopic third ventriculostomy at infected cerebrospinal fluid shunt removal. *J Neurosurg Pediatr*. 2012;9(3):320-326.
39. Stovell MG, Zakaria R, Ellenbogen JR, et al. Long-term follow-up of endoscopic third ventriculostomy performed in the pediatric population. *J Neurosurg Pediatr*. 2016;17(6):734-738.
40. Tamburrini G, D'Angelo L, Paternoster G, Massimi L, Caldarelli M, Di Rocco C. Endoscopic management of intra and paraventricular CSF cysts. *Childs Nerv Syst*. 2007;23(6):645-651.
41. Zhao R, Shi W, Yang H, Li H. endoscopic third ventriculostomy instead of shunt revision in children younger than 3 years of age. *World Neurosurg*. 2016;88:92-96.
42. Bouras T, Sgouros S. Complications of endoscopic third ventriculostomy. *J Neurosurg Pediatr*. 2011;7(6):643-649.
43. Waqar M, Ellenbogen JR, Mallucci C. Endoscopic third ventriculostomy for shunt malfunction in children: a review. *J Clin Neurosci*. 2018;51:6-11.
44. Warf BC. Hydrocephalus in Uganda: the predominance of infectious origin and primary management with endoscopic third ventriculostomy. *J Neurosurg*. 2005;102(1 suppl):1-15.
45. Buxton N, Macarthur D, Robertson I, Punt J. Neuroendoscopic third ventriculostomy for failed shunts. *Surg Neurol*. 2003;60(3):201-204.
46. Siomin V, Cinalli G, Grotenhuis A, et al. Endoscopic third ventriculostomy in patients with cerebrospinal fluid infection and/or hemorrhage. *J Neurosurg*. 2002;97(3):519-524.
47. Teo C, Jones R. Management of hydrocephalus by endoscopic third ventriculostomy in patients with myelomeningocele. *Pediatr Neurosurg*. 1996;25(2):57-63.
48. Talamonti G, Nichelatti M, Picano M, Marcati E, D'Aliberti G, Cenzato M. Endoscopic third ventriculostomy in cases of ventriculoperitoneal shunt malfunction: does shunt duration play a role? *World Neurosurg*. 2019;127:e799-e808.
49. Neils DM, Wang H, Lin J. Endoscopic third ventriculostomy for shunt malfunction: what to do with the shunt? *Surg Neurol Int*. 2013;4:3.
50. Furlanetti LL, Santos MV, de Oliveira RS. The success of endoscopic third ventriculostomy in children: analysis of prognostic factors. *Pediatr Neurosurg*. 2012;48(6):352-359.
51. Peretta P, Cinalli G, Spennato P, et al. Long-term results of a second endoscopic third ventriculostomy in children: retrospective analysis of 40 cases. *Neurosurgery*. 2009;65(3):539-547.
52. O'Brien DF, Javadpour M, Collins DR, Spennato P, Mallucci CL. Endoscopic third ventriculostomy: an outcome analysis of primary cases and procedures performed after ventriculoperitoneal shunt malfunction. *J Neurosurg*. 2005;103(5 suppl):393-400.
53. Schroeder HW, Niendorf WR, Gaab MR. Complications of endoscopic third ventriculostomy. *J Neurosurg*. 2002;96(6):1032-1040.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Lee, Aquilina. Acquisition of data: Lee, Chari, Gillespie. Analysis and interpretation of data: Lee, Chari, Saffari, Aquilina. Drafting the article: Lee, Aquilina. 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: Lee. Statistical analysis: Lee, Saffari. Administrative/technical/material support: Lee. Study supervision: Lee, Saffari, James, Aquilina.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplementary Tables and Figures. https://thejns.org/doi/suppl/10.3171/2023.1.PEDS22427.

Correspondence

Keng Siang Lee: Great Ormond Street Hospital for Children, London, United Kingdom Developmental Neurosciences, Great Ormond Street Institute of Child Health, University College London, London, United Kingdom. mrkengsianglee@gmail.com.