The efficacy of endoscopic third ventriculostomy in children 1 year of age or younger: A systematic review and meta-analysis

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Purpose: Hydrocephalus is a major cause of morbidity in the pediatric population, with potentially severe consequences if left untreated. Two viable strategies for management of non-communicating hydrocephalus are endoscopic third ventriculostomy (ETV) and ventriculoperitoneal shunting. However, there is uncertainty over the safety and efficacy of ETV in younger infants aged 1 year or below. In this systematic review, we aim to elucidate the success rate and procedural risks of ETV in this age group.
Methods: A multi-database (PubMed, Embase, Web of Science) literature search between January 1990 and April 2018 was performed in accordance with PRISMA guidelines. Eligible studies were included if they (i) examined non-communicating hydrocephalus; (ii) quantified the success/failure rates of ETV; and (iii) assessed outcomes in children 1 year of age or younger.
Results: A total of 19 articles with 399 patients were eligible for inclusion. Mean age at procedure was 4.2 months (range 34 weeks gestation to 12 months), with 116 females and 143 males. Commonest underlying aetiology was congenital aqueductal stenosis (AS) (60.4%). Remaining causes included posthaemorrhagic, post-infection, Chiari malformations, malignancies and others. Overall and AS mean success rates were 51.6% and 56.5% respectively. Overall complication rate was 10.0%, consisting mainly of CSF leak, infection, and haemorrhage. Younger age was significantly associated with poorer ETV success rate when divided into <6 months and 6e12 months of age (44.4 vs 66.7%; p ¼ 0.0007). Underlying pathology had no significant association with ETV outcome when divided into AS and other pathologies (p ¼ 0.53).
Conclusions: Age is significantly associated with ETV success rates. Pathology-dependent effects were not found in this age group. Despite a lower ETV success rate at younger ages (44.4 vs 66.7%), it offers a comparable safety profile that is independent of age. ETV remains a viable treatment option for noncommunicating hydrocephalus for infants aged 1 year or younger.

1. Introduction

Hydrocephalus is a major cause of morbidity in the paediatric population, with an estimated prevalence of 1.2 in every 1000 children [1]. It is estimated to account for approximately half of all paediatric neurosurgical cases managed in the UK [2]. In children, untreated hydrocephalus can have severe consequences including developmental problems, learning difficulties, and blindness [3]. Hydrocephalus can be classified as communicating or noncommunicating, depending on the level of obstruction to CSF flow. This classificationwas

first proposed byWalter Dandy in 1918 [4], and the distinction between the two categories was related to exit of CSF from the fourth ventricle.

Traditionally, shunts have been used as the main treatment strategy for both communicating and non-communicating hydrocephalus. More recently, endoscopic third ventriculostomy (ETV) has emerged as a method of treatment for hydrocephalus [3,5]. The first ETV was actually performed in 1923 by the urologist, William Mixter, who performed the procedure on a child with obstructive hydrocephalus using a urethroscope [6]. However, this procedure was not widely adopted until the 1980's, when advancements in equipment ensured that itwas safer/more successful [7]. Shunts are associated with significant complications, such that they are thought to occur in close to40% of shunted patients, and they include failure and infection [8,9]. In contrast, ETV, which does not involve the insertion of foreign bodies into the central nervous system (CNS), is associated with a lower complication rate (<10%) [10].

Currently, both ETV and shunting are viable strategies for treating non-communicating hydrocephalus. While patient age is believed to be an important factor when it comes to shunting, it is not entirely clear if there is a cut-off age below which ETV cannot be performed safely and, if so, what that is [11]. Much controversy remains over whether children younger than 1 year of age are at greater risk of ETV failure/complications compared with older patients [12]. The aim of this studywas to perform a systematic review/ meta-analysis on the published literature on ETV in children aged 1 year or younger, in order to elucidate the success rate of this procedure in this particular patient population.

2. Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement was used to prepare this paper [13]. The protocol for this systematic review is registered on PROPSERO (CRD42018081949).

2.1. Literature search

A multi-database (PubMed, Embase, Web of Science) literature search between January 1990 and April 2018 was performed by authors SM and AH. Conflict of opinionwas settled by senior author PL. The search terms used were: non-communicating/obstructive hydrocephalus AND (“endoscopic third ventriculostomy” or ETV) AND (child OR children OR infants). Only articles in English were included in the search. The bibliographies of identified papers were examined in order to identify any further relevant articles.

2.2. Literature selection

Articles were identified according to the aforementioned criteria, and all titles and abstracts were reviewed. Eligible studies were included if they satisfied all of the following criteria: (1) examine non-communicating/obstructive hydrocephalus; (2) quantify the success/failure rates of ETV; and (3) assess outcome in children 1 year of age or younger. Underlying pathology was also noted. In cases where pathologies typically associated with communicating hydrocephalus were present, patients were still included if the article categorized them as obstructive. Any uncertainties were resolved by discussion with the senior author (PL).

2.3. Data extraction/analysis

The following data were extracted from the selected papers by authors SM and FS: (1) number of subjects; (2) mean age of patients; (3) sex of patients; (4) the underlying aetiology of the noncommunicating hydrocephalus; (5) the exact intervention performed; (6) the number of successful cases; (7) the percentage of successful cases; (8) average time at follow-up; (9) number of cases in which complications were recorded; and (10) the percentage of cases in which complications were recorded. ETV success was defined as the avoidance of VP shunting in our analyses, consistent with the majority of studies (see Results). Meta-analysis was performed using Microsoft Excel v16.24, using the Chi square test to evaluate the effects of underlying pathology and age on ETV success.

2.4. Assessment for bias

Risk of bias was analyzed by three senior authors (MZ, CP, and IB) using the risk of bias in non-randomized studies e of interventions (ROBINS-I) assessment tool [14] (see Table 1).

3. Results

A total of 629 articles were generated. Four additional articles were identified upon reviewing bibliographies of relevant articles. In total, 614 articles were excluded, thus leaving 19 articles for subsequent analysis (see Fig. 1). The reasons for exclusion were: (1) articles were not original research; (2) did not feature noncommunicating hydrocephalus or also featured communicating hydrocephalus; (3) did not consider patients 1 year of age or younger; and/or (4) considered choroid plexus cauterization (CPC) combined with ETV as a treatment for hydrocephalus. Two studies were extensions of previous publications from the same group, therefore only one of each was included for further analysis, based on meaningful data regarding demographics and outcome elucidated in each study [15,16].

Table 1
Summarises risk of bias of included studies.

	Study	Confounding	Selection	Intervention classification	Deviation from intervention	Missing data	Measurement of outcome	Selection of reported result	Overall
1	Tewuerbati et al., 2015	Moderate	Moderate	Low	Low	Low	Low	Low	**Moderate**
2	Zohdi et al., 2013	Serious	Serious	Moderate	Low	Low	Low	Moderate	**Serious**
3	El Beltagy et al., 2010	Critical	Serious	Low	Low	Low	Low	Moderate	**Critical**
4	Gallo et al., 2010	Serious	Low	Low	Low	Low	Low	Moderate	**Serious**
5	Ogiwara et al., 2010	Critical	Low	Low	Low	Moderate	Low	Moderate	**Critical**
6	Lipina et al., 2008	Critical	Low	Low	Low	Low	Low	Moderate	**Critical**
7	Baldauf et al., 2007	Critical	Low	Low	Low	Low	Low	Moderate	**Critical**
8	Yadav et al., 2006	Serious	Low	Low	Low	Low	Low	Moderate	**Serious**
9	Fritsch et al., 2005	Serious	Low	Low	Low	Low	Low	Moderate	**Serious**
10	Warf et al., 2005	Serious	Low	Low	Low	Critical	Low	Low	**Critical**
11	Gorayeb et al., 2004	Serious	Low	Low	Low	Low	Low	Moderate	**Serious**
12	Koch and Wagner, 2004	Moderate	Low	Low	Low	Low	Low	Low	**Moderate**
13	Javadpour et al., 2001	Serious	Low	Low	Low	Low	Low	Low	**Serious**
14	Murshid et al., 2000	Serious	Low	Low	Low	Low	Low	Low	**Serious**
15	Kim et al., 2000	Serious	Low	Low	Low	Low	Low	Low	**Serious**
16	Hopf et al., 1999	Serious	Low	Low	Low	Low	Low	Low	**Serious**
17	Goumnerova et al., 1997	Critical	Low	Low	Low	Low	Low	Low	**Critical**
18	Kunz et al., 1994	Critical	Low	Low	Low	Low	Low	Low	**Critical**
19	Jones et al., 1990	Critical	Low	Low	Low	Low	Low	Low	**Critical**

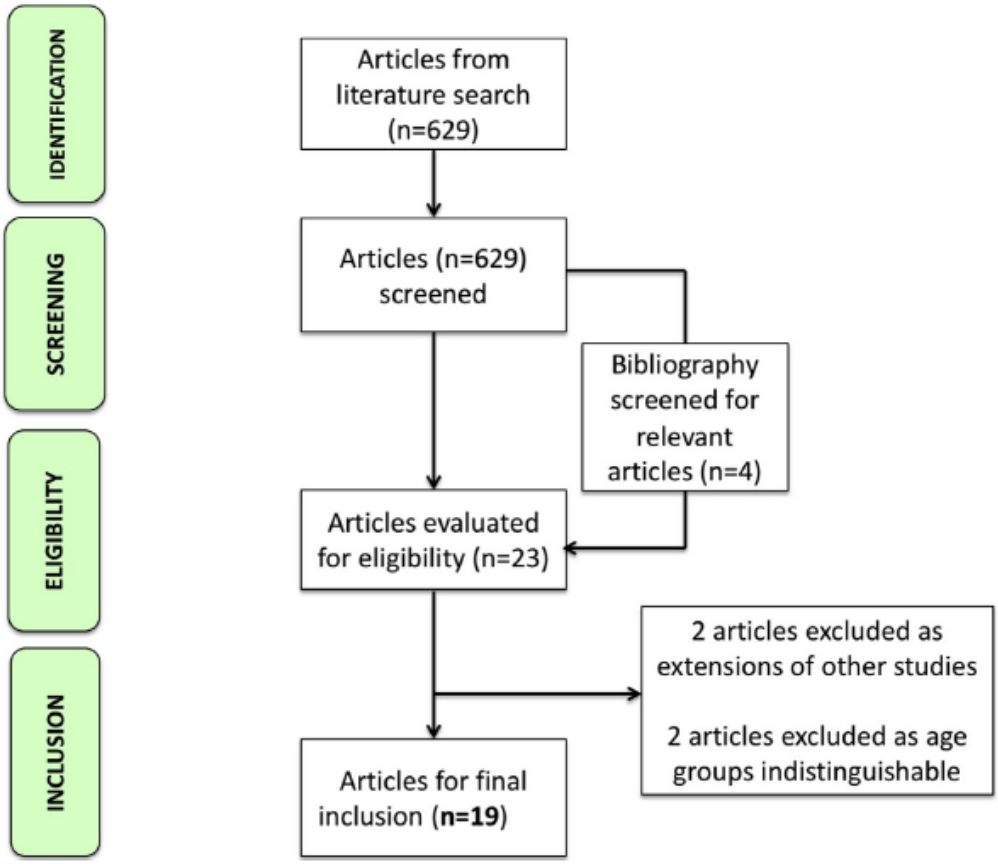

Fig. 1. Depicts methodology flow chart in accordance with PRISMA guidelines.

3.1. Demographics

In total, 19 studies [15e33] were eligible for final inclusion (see Table 2). A total of 399 patients were evaluated. The mean ageacross 190 patients, where age was individually stated, was 4.2 months (range 34 weeks gestation to 12 months). Of the 256 patients whose genders were stated, 116 were female while 143 were male. The most common underlying aetiology of the noncommunicating hydrocephalus was congenital aqueductal stenosis, which accounted for 50% of all cases (177 out of 399). Remaining causes of hydrocephalus included post-haemorrhagic (35; 8.8%), post-infection (83; 20.8%), Chiari malformation (16; 4.0%), malignancy (6; 1.5%), Dandy Walker malformation (5; 1.3%), intracranial cysts (5; 1.3%), myelomeningocele (3; 0.8%), CNS malformation (2; 0.5%), Galen malformation and occipital encephalocele (1; 0.3% each). Aetiology was unspecified in 11.8% of patients (47 patients).

Table 2
Summarises key characteristics of included studies.

Study	Number of subjects	Mean age (months)	Seks	Aetiology of non-communicating hydrocephalus	Intervention	Number of successful cases	Success rate (%)	Average time at follow-up (months)	Number of cases in which complications were recorded	Complication rate (%)
Tewuerbati et al., 2015	44	5.7	24F: 20 M	Congenital obstructive (not specified): 44	ETV: 44	16	36.4	N/A	9 (5 seizure; 3 infection; 1 subdural haemorrhage)	20.5
Zohdi et al., 2013	8	2.5 (range: 1 month to 4 months)	N/A	Aqueductal stenosis: 8	ETV: 8	1	12.5	4.0 (range: 1 week to 24 months)	1 (CSF leak + cardiac failure)	12.5
El Beltagy et al., 2010	3	12	N/A	Posterior fossa tumor (ependymoma: 2; medulloblastoma: 1)	ETV: 3	0	0	N/A	N/A	N/A
Gallo et al., 2010	23	2.7 (range: 1 day to 170 days)	12F: 11 M	Aqueductal stenosis: 10; posterior fossa cyst: 3; Dandy-Walker malformation: 2; posthemorrhagic: 4; occipital encephalocele: 1; Chiari I malformation: 1; quadrigeminal cyst: 1; other: 1	ETV: 20; ETV + endoscopic cystocisternostomy (ECC): 3	9	39.1	49.3 (range: 6–84 months)	2 (1 post-operative seizures; 1 intraoperative forniceal injury)	8.7
Ogiwara et al., 2010	23	2.9 (range: 5 days–158 days)	9F: 14 M	Aqueductal stenosis: 11; posthemorrhagic: 6; myelomeningocele: 2; postmeningitis: 2; Chiari I malformation: 1; Dandy-Walker malformation: 1	ETV: 23	8	34.8	57.4 (range: 3–106 months)	3 (1 intraventricular haemorrhage; 1 meningitis and CSF leak; 1 meningitis alone)	13
Lipina et al., 2008	14	3.5 (range: 58 days–168 days)	6F: 8 M	Aqueductal stenosis: 5; posthemorrhagic: 8; posthemorrhagic/postinfectious: 1	ETV: 14	8	57.1	21 (range: 10–33 months)	1 (subdural hygroma)	7.1
Baldauf et al., 2007	16	4.0 (range: 0.5 months–11 months)	N/A	Aqueductal stenosis: 7; other congenital anomaly: 3; tumor: 2; post hemorrhagic: 4	ETV: 16	6	37.5	N/A	N/A	N/A
Fritsch et al., 2005	8	5.6 (range: 19 days–347 days)	4F: 4 M	Aqueductal stenosis: 3; myelomeningocele: 4; Dandy-Walker malformation: 1	ETV: 8	6	75	42.6 (range: 18–89 months)	N/A	N/A
Warf et al., 2005	106	<1 year	N/A	Post-infectious: 63; aqueductal stenosis of unspecified cause: 23; myelomeningocele: 20	ETV: 106	63	59.4	N/A	N/A	N/A
Gorayeb et al., 2004	36	4.7 (range: 3 days to 11 months)	17 M: 19F	Aqueductal stenosis: 11; Chiari type II malformation: 11; other: 14	ETV: 36	23	63.9	47.4 (range: 22–69 months)	4 (not specified)	11.1
Koch and Wagner, 2004	16	4.5 (range: 8 days–311 days)	8F: 8 M	Aqueductal stenosis: 16 (idiopathic: 7; posthemorrhagic: 3; postmeningitic: 4; CNS/vascular malformation: 3)	ETV: 16	5	31.3	Done in 5 cases: 29.2 (range: 16–52 months)	3 (2 CSF leakage; 1 minor intraoperative venous bleed)	18.8
Javadpour et al 2001	21	1.5 (range: birth to 10 months)	13 M: 8F	Intra-ventricular haemorrhage: 27, aqueductal stenosis: 7, meningitis: 4, spina bifida: 1 other: 4	ETV: 21	7	33.3	18 (range: 8–36 months)	2 (CSF leak, transient hyponatraemia)	9.5
Kim et al 2000	6	6.2 (range: 1–11 months)	2 M: 4F	Aqueductal stenosis: 4, intraventricular haemorrhage: 1, shunt infection: 1	ETV: 6 (previous VP shunt in 1)	2	33.3	14.3 (range: 3–50 months)	2 (occulo-motor nerve palsy)	33.3
Murshid et al 2000	13	5.8 (range: birth to 12 months)	11 M: 2F	Aqueductal stenosis: 5, post ventriculitis: 5, intracranial cyst: 2, Dandy Walker malformation: 1	ETV: 13 (previous VP shunt in 6)	9	69.2	N/A	8 (SDH, DI, wound infection, pyrexia, IVH, oculomotor and abducens nerve palsies)	61.5

3.2. ETV outcomes

ETV was the first surgical procedure in the majority of patients (385; 96.5%). Of the patients with prior failed procedures, 1 patient had an aqueductoplasty, and the remaining 13 patients had VP shunts. In 0.8% of cases (3 out of 399 cases), ETVwas combined with endoscopic cystocisternostomy (ECC). Included studies had minor variation on their definition of success, but avoidance of shunting was the predominant theme (see Table 3). The mean success rate across all patients was 51.6% (206 out of 399 cases). Mean success

rate in primary aqueductal stenosis was 56.5% (100 out of 177 cases), whilst other pathologies had a mean success rate of 53.1% (93 out of 175 cases) (see Table 4). However, underlying pathology had no significant association with ETV outcome (Chi sq test, pvalue 0.53, see below).

Out of 399 patients, only 40 (10.0%) were reported to have post-operative complications, outside of procedural failure. The complications, in descending order of prevalence, were: postoperative pyrexia (10; 25%); CSF leak (6; 15%); meningitis (4; 10%); subdural haematoma, wound infection, oculomotor nerve palsy, and intra-ventricular haemorrhage (3; 7.5%); diabetes insipidus (2; 5%); abducens nerve palsy, transient hyponatraemia, CSF fistula, transient Parinaud's syndrome, seizures, and forniceal injury (1; 2.5% each). Duration of follow up was reported for 207 patients, with an average duration of 27.0 months (range 1 weeke106 months).

3.3. Risk factors

Age was significantly associated with ETV outcomes when divided into <6 months and 6e12 months of age (Chi sq 11.6, Df 1, p-value 0.0007) (see Table 5), demonstrating better outcomes in the older age group. Underlying pathology had no significant association with ETV outcome when comparing primary aqueductal stenosis with other pathologies (Chi sq 0.40, Df 1, p-value 0.53).

4. Discussion

Neurosurgical reports on which patients are most expected to benefit from ETV are ample and contradictory. The debate largely focuses on the success rates, the influence of age, aetiology or both. Some neurosurgeons advocate ETV as the treatment of choice for non-communicating hydrocephalus caused by primary aqueductal stenosis and other selected pathologies [34]. Indeed, ETV was performed as a first line procedure in 96.5% of patients included in this study. However, whether children younger than 1 year of age are at greater risk of ETV failure compared with older patients remains contentious.

The mean success rate was 51.6% across all included studies. Reported success rates across included studies ranged from 0% [29] to as high as 83% [25]. Some studies found lower success rates in younger patients [20,30,32], although the differences were not always statistically significant [16,25,35]. One study found a pathology dependent effect rather than an age dependent effect on outcomes of ETV, where patients with congenital aqueduct stenosis had better outcomes than other categories [22]. Both an age and aetiology dependent outcome were reported by four studies [24,26,28],39. One study found that younger patients with aqueductal stenosis and Chiari malformation had statistically significant worse outcomes [24]. The remaining studies found that older infants with aqueductal stenosis yielded better outcomes [26,28]. However, statistical analyses were not performed, likely due to the small sample size, which was acknowledged by the authors.

Kulkarni et al. developed the ETV Success Score (ETVSS) in children [36]. This prediction model provides a simple method for predicting success of ETV at 6 months. The score is based on 3 factors; listed in order of magnitude: patient age, aetiology of hydrocephalus, and the presence or absence of a previous shunt. The highest rate of success is found in older children with aqueduct stenosis or tectal tumor who have not had previous shunting.

The ETVSS has been externally validated in a number of studies [37e39]. However, ETV still fails in certain patients, despite being the best candidates for the procedure according to the prediction model [40].

Success rates were notably lower in earlier studies. As with any procedure, a learning curve is expected. It is possible that a gradual improvement in outcomes will occur as the cumulative experience increases over time. Operative details were notably absent in 7 of the 18 studies. Future studies are advised to report on surgical details, as they may be vital in determining success of ETV.

Despite encompassing a relatively large number of patients (n ¼ 399), included studies demonstrate both clinical and methodological heterogeneity. For example, there is variability in the definition of successful outcomes, length of follow up, surgical technique and diagnostic imaging used. All studies except two were found to have critical or serious risks of bias. The two exceptions encompassed 60 patients (20.4% of total). Also, the majority of studies were of retrospective design. Methodological concerns common to retrospective studies include selection bias, publication bias and incomplete data.

Table 3
Summarises definition of ETV success across included studies.

Study	Definition
Tewuerbati et al., 2015	Clinical resolution and no requirement for further neurosurgical treatment
Zohdi et al., 2013	No formal definition
El Beltagy et al., 2010	No requirement for VP shunt within first year post ETV
Gallo et al., 2010	No requirement for VP shunt
Ogiwara et al., 2010	Clinical resolution and no requirement for VP shunt
Lipina et al., 2008	No requirement for VP shunt
Baldauf et al., 2007	No requirement for VP shunt
Yadav et al., 2006	Anterior fontanelle depressed or flush to adjoining scalp, and patient improved clinically
Fritsch et al., 2005	Clinical and radiological resolution, with no requirement for VP shunt
Warf et al., 2005	No requirement for VP shunt
Gorayeb et al., 2004	Clinical improvement of pre-operative signs and symptoms, stable head growth, and normal radiological findings
Koch & Wagner 2004	No further surgical procedure necessary, stable or decreasing head circumference, decreasing ventricular size on ultrasound, no clinical signs of raised intracranial pressure
Javadpour et al., 2001	Clinical improvement of pre-operative signs and symptoms, and stable head growth
Kim et al., 2000	Resolution of clinical symptoms or slowing of head growth rate
Murshid et al., 2000	Clinical improvement of pre-operative signs and symptoms
Hopf et al., 1999	Partial or complete relief of symptoms
Goumenova et al., 1997	No formal definition
Kunz et al., 1994	No formal definition
Jones et al., 1990	Not shunt dependent, normal head growth, and no clinical/radiological evidence of raised intracranial pressure

An important issue to consider when deciding whether ETV is a suitable treatment option in children aged one year or under is its cost compared to other techniques. A study examining the cost/ benefit ratio of ETV compared with shunting found no statistically significant difference between the two treatment strategies, though there was a trend towards an improved cost/benefit ratio with ETV compared with shunting [1]. However, further studies, focusing on the patient cohort that this review examined, are required to determine whether ETV is a cost-effective treatment option for hydrocephalus in this particular patient group.

Table 4
ETV success rate across different underlying pathologies (AS- aqueductal stenosis, IVH- intraventricular haemorrhage, PNET-primitive neuro-ectodermal tumour).

Pathology	ETV Success (n, %)
Primary AS	100 (56.4)
Chiari I	5 (41.7)
Chari II	2 (50)
Dandy Walker	1 (20)
IVH	15 (42.9)
Infection (non specified)	11 (55)
Meningitis	47 (67.1)
Ventriculitis	3 (60)
TB meningitis	5 (62.5)
Myelomeningocele	8 (38.1)
Occipital encephalocele	1 (100)
Malignancy	2 (33.3)
Posterior fossa PNET	2 (100)
Ependymoma	0 (0)
Medulloblastoma	0 (0)
Intracranial cysts	4 (80)
Post fossa cyst	1 (50)
Sylvian cyst	1 (100)
Suprasellar cyst	2 (100)
CNS malformation	0 (0)
Galeni malformation	0 (0)

Table 5
Summarises statistical analysis of ETV success with respect to underlying pathology (AS- aqueductal stenosis, ETV- endoscopic third ventriculostomy, NS- non-significant, p-value < 0.001*** using chi-square test).

Patients, n (%)	ETV success	ETV failure	Chi sq, Df, p-value
Pathology			
Primary AS	100 (56.5)	77 (43.5)	0.40, 1, 0.53 (NS)
Other	43 (45.7)	51 (54.3)	–
Age group			
0–6 months	80 (44.4)	100 (55.6)	11.6, 1, 0.0007***
6–12 months	58 (66.7)	29 (33.3)	–

This systematic review has a number of limitations. Firstly, by excluding articles published in languages other than English, it may be that a number of relevant articles were missed. Similarly, the search terms we used may have limited the number of articles that the search generated, therefore resulting in omission of some relevant articles. However, examination of the bibliographies of relevant articles only brought up a further four articles that were included in the review. One key issue was defining ETV success, which varied between included articles (Table 3). Given that the majority of articles included the absence of requirement for VP shunt insertion as a criterion for ETV success, we adopted this in the evaluation of the cohort. Although this dichotomization is pragmatic, variability in the duration of follow up affects the validity of this measure. Indeed, whilst the mean follow-up period was 27 months, a wide range was reported, from 1 week to 106 months. Therefore, it is difficult to determine the long term outcomes of ETV in our chosen patient population, given that ETV failure is thought to increase with longer follow up periods [5]. Future studies require longer duration of follow up and stricter definitions for ETV success in this age group. A further limitation of this systematic review is the fact that, while the majority of patients underwent ETV alone, a small minority underwent ETV coupled with ECC. ECC is likely to alter the efficacy of ETV when compared with ETV alone, which may hinder direct comparisons. Finally, more than half of the cases included in this review were due to

primary aqueductal stenosis, with a much smaller proportion resulting from other aetiologies. For instance, the inclusion of infants with malignant brain tumours and the associated poor prognosis may skew the proposed ETV success rate. This limits the validity of this systematic review in determining the efficacy of ETV as a treatment for noncommunicating hydrocephalus secondary to etiologies other than aqueductal stenosis. Finally, it should be noted that some potentially eligible patients may have been excluded as part of a subgroup with insufficient data, restricting the cohort that was studied.

5. Conclusion

Our systematic review shows that ETV is successful in just over half of all included cases of non-communicating hydrocephalus. Despite higher success rates for aqueductal stenosis at 56.5%, we found no statistically significant pathology-dependent effect on ETV success rate. We report an overall complications rate of 10.0%, with CSF leak, haemorrhage, and infection being the most frequently encountered complications. Despite a lower success rate at younger ages, ETV offers a comparable safety profile that is independent of age. Therefore, ETV may remain a viable treatment option for non-communicating hydrocephalus for infants aged 1 year or younger.

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