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ORIGINAL ARTICLE

Success and complication rates of endoscopic third ventriculostomy for tuberculous meningitis: a systematic review and meta-analysis

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Abstract

Because ventriculoperitoneal shunt (VPS) insertion for patients with hydrocephalus from tuberculous meningitis (TBM) can be complicated by shunt infection and malfunction, endoscopic third ventriculostomy (ETV) has been proposed as an alternative. The aim of this review was to determine the success, technical failure, and complication rates of ETV in TBM in a meta-analysis and determine which factors are predictive of outcome. The PubMed, Scopus, and CENTRAL databases were searched from inception to April 2020 for case series, cohort studies, or randomized controlled trials reporting success, technical failure, or complication rates. For studies with individual patient data available, logistic regression analysis was done to determine whether age, sex, clinical grade, and type of hydrocephalus on imaging was predictive of outcome. Eight studies with a total of 174 patients were included in the review. Using random-effects modeling, the pooled estimate of success rate was 59% (95% CI 50–68%), with low heterogeneity ($I^2 = 30\%$). The technical failure and complication rates were 5% and 15%, respectively, but these variables had moderate heterogeneity. In 36 patients with individual patient data, a non-communicating type of hydrocephalus on imaging was associated with an odds ratio of 5.90 (95% CI 1.1–32.9, $p = 0.043$) for success. In summary, ETV for TBM had a pooled success rate of 59%, technical failure rate of 5%, and complication rate of 15%. An imaging finding of non-communicating hydrocephalus was associated with increased success. High-quality randomized, prospective studies using VPS insertion as control are needed to further define the role of ETV in TBM.

Keywords Endoscopic third ventriculostomy · Tuberculous meningitis · Hydrocephalus

Introduction

Tuberculous meningitis (TBM) is a severe extrapulmonary form of tuberculosis which affects an estimated 100,000 individuals annually [21]. Among its most common complications is hydrocephalus which occurs in up to 70% of patients with the disease [6]. The type of hydrocephalus in TBM may be communicating, non-communicating, or mixed. It is of the communicating type in up to 82% of individuals, as the presence of thick exudates in the basal cisterns obstructs CSF flow in the subarachnoid spaces and the arachnoid granulations [6, 13, 19, 20]. Less commonly, hydrocephalus may be non-communicating and results from exudates, leptomeningeal scarring, or tuberculomas causing obstruction within the ventricular system, commonly at the level of the fourth ventricular outlet foramina or the aqueduct of Sylvius [19, 27].

The mainstay in the treatment of medically refractory hydrocephalus in TBM is insertion of a ventriculoperitoneal shunt [2, 9, 23]. However, shunt insertion is not innocuous and is associated with hardware-related complications, including infections, shunt erosions, and malfunctions requiring repeated revisions [2, 9, 19, 22, 23]. TBM, in particular, is believed to be associated with an increased incidence of shunt

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obstruction due to the high cellularity and protein content of the patients' cerebrospinal fluid [2, 9, 22].

An attractive alternative to VPS insertion is endoscopic third ventriculostomy. While initially thought to be effective only for obstructive types of hydrocephalus, recent studies have shown its efficacy in communicating hydrocephalus [17, 25]. In one study, success rates of 60.9% and 64.3% were reported for post-hemorrhagic and post-infectious hydrocephalus, respectively [25]. Data for its role in tuberculous meningitis has been sparse, with only a few small retrospective and prospective series on the topic.

We aimed to perform a systematic review of the literature for studies assessing the success, technical failure, and complication rates of endoscopic third ventriculostomy for tuberculous meningitis-associated hydrocephalus. A secondary objective was to determine whether factors such as age, sex, clinical grade, and type of hydrocephalus are predictive of outcome.

Methods

Criteria for selection of studies

Articles in the English language published from the databases' date of inception until March 20, 2020, were eligible. The inclusion criteria were the following: (1) the articles described as either a case series, cohort, or randomized controlled trial; (2) studies included patients with tuberculous meningitis complicated by communicating or non-communicating hydrocephalus diagnosed with either a CT scan or MRI, with clinical manifestations of increased ICP; (3) subjects in a group who underwent completed or attempted endoscopic third ventriculostomy; and (4) outcomes included either complication rates or post-operative success rates. "Success" can be defined as either (1) no need for further CSF diversion surgery, (2) resolution of symptoms of increased intracranial pressure or clinical improvement, or (3) decrease or stability in ventricular size on post-operative imaging. Studies were excluded if (1) subjects had an alternative diagnosis other than tuberculous meningitis or had known multiply drug-resistant tuberculosis; (2) subjects had previous CSF diversion surgery (shunt insertion or previous ETV); (3) other procedures were performed in addition to ETV (e.g., choroid plexus coagulation, lamina terminalis fenestration, monroplasty, septostomy, or lumboperitoneal shunt); or (4) studies were repeat publications of previously reported data.

Search methods for the identification of studies

Guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement, we performed a systematic search of the Scopus, PubMed, and the Cochrane Central Register of Controlled Trials (CENTRAL) databases [18]. We used the following terms and synonyms: "endoscopic third ventriculostomy" AND "tuberculous meningitis."

Selection of studies

Two reviewers (AO and AE) screened all studies based on study titles and abstracts. Disagreements were resolved through consensus. The studies were evaluated independently.

Data extraction and outcome measures

The following data were collected using piloted data extraction forms: authors, publication year, number of subjects, age range of subjects, type of hydrocephalus reported in subjects (communicating, non-communicating, or both), criteria used to define ETV success, and average length of follow-up.

The primary outcome measures were the rates of successes, technical failures, and complications. A successful case is one who met the criterion/-ia set by the study. A technical failure is a case in which endoscopic third ventriculostomy was attempted but not completed due to difficult third ventricular floor anatomy or other intraoperative issues. Complications were assessed using the Landriel Ibanez Classification: grade I or mild complications were any non-life-threatening deviation from the normal post-operative course not requiring invasive treatment; grade II or moderate complications required invasive treatment such as surgical, endoscopic, or endovascular interventions; grade III or severe complications were life-threatening and required critical care management; and grade IV complications were fatal [14].

For studies reporting individual patient data, the following were collected for each patient: age, sex, type of hydrocephalus, Vellore grade, and outcome (success or failure).

Quality assessment/risk of bias

We independently assessed the studies for quality and risk of bias. Randomized controlled trials (RCT) were assessed with the Cochrane Risk of Bias assessment tool for RCTs [12]. Cohort and case-control studies were evaluated using the Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis [26]. The NOS evaluates studies on three domains—patient selection, comparability, and assessment of outcome—and allocates scores of 0–9 for each study. Studies scoring at least 6 were considered to be of high quality.

Statistical analysis

Categorical variables were summarized using frequencies and proportions and continuous variables using means and standard deviations or median and ranges. For the obtained individual data available, we performed logistic regression to evaluate the association between potential predictors such as age, sex, type of hydrocephalus, and Vellore grade to outcomes of ETV (success or failure). Descriptive statistics and logistic regression were performed using the Stata/MP Version 14.0 for Mac (College Station, TX: StataCorp LP). Effect estimate used was odds ratio with statistical significance detected if the 95% confidence interval does not include the number 1.

Quantitative synthesis of data from the included studies was conducted for studies with > 5 enrolled patients. Meta-analysis of proportions was performed using R (Version 3.6.3) with the following packages: *meta*, *metafor*, and *weightr*. The unit of analysis was the individual patient. Random-effects analyses of proportions were estimated using the DerSimonian and Laird method. Chi-square test was used to detect statistical heterogeneity with p value set < 0.10. To assess the degree of heterogeneity, I^2 statistics were computed with > 25%, > 50%, and > 75% set to indicate low, moderate, or high degree of heterogeneity, respectively. Publication bias was assessed visually by constructing funnel plots and quantitatively by Egger's regression test with p value set at < 0.05.

Results

Included studies

A total of 65 records were identified through the database search. After duplicates were removed, 43 articles were screened. Of these, 23 articles were excluded because they were irrelevant or did not meet the inclusion criterion for study design. The full text of 20 articles were assessed, of which, 12 articles were excluded for the reasons stated above. Eight studies were included in the qualitative analysis and meta-analysis. Three of these studies had breakdown of individual data and were included in the individual patient data meta-analysis (Fig. 1).

One of the studies included was a randomized controlled trial; four studies were prospective cohort studies, while three studies were retrospective cohort studies. All studies were done after 2005, with the most recent cohort reported in 2014. The age range of patients varied among the studies, with 5 including both pediatric and adult patients, 2 studies reporting pediatric data, and 1 study including infants only. Studies included between 6 and 59 (median: 17) subjects.

All studies reported ETV success rates although the exact definition of success varied; 7 out of 8 reported technical failure rates; and half of the studies included data on complications. The weighted mean follow-up for studies in which this information was available was 5.5 months (range: 2.4–8 months). All the studies' characteristics are summarized in Table 1.

Methodological quality assessment for the included studies

The sole randomized controlled trial included in the meta-analysis had a cohort of patients treated instead using VPS insertion as a control group. The RCT was assessed as having high risk for both performance and detection bias due to non-blinding of the participants and researchers to the intervention and the outcomes assessment (Supplemental Table 1).

None of the observational studies had a control cohort. Five of the seven were assessed to have good quality, defined as an NOS score of at least 6. Two of the studies had a score of 5 due to age inclusion criteria which limited its applicability to the population at large (Supplemental Table 2). Figaji et al. included only pediatric patients, while Yadav et al. limited the analysis to only infants [8, 27].

Random-effects meta-analysis of success, technical failure, and complication rates

The studies yielded a total of 174 subjects with TBM who underwent endoscopic third ventriculostomy. Using random-effects modeling, the estimate of success rate was 59% (95% CI 50–68%). There was low heterogeneity for this variable in the included studies ($I^2 = 30\%$) (Fig. 2). The estimate for technical failure rate was 5% (95% CI: 0–17%), with moderate heterogeneity ($I^2 = 70\%$) (Fig. 3). The total complication failure rate estimate was 19% (95% CI: 8–40%), with moderate heterogeneity (95% CI: 71%) (Fig. 4). Most of the complications were graded mild-moderate according to the Landriel-Ibanez Classification, with a pooled estimate of 15% (95% CI 6–33%; $I^2 = 63\%$).

The funnel plots for all variables did not demonstrate gross asymmetry (Fig. 5). This is consistent with results of the Egger's tests, which were all non-significant ($p = 0.3887$ for success rate; $p = 0.2539$ for technical failure rate; and $p = 0.6555$ for complication rate). These findings support the absence of significant publication bias in the included studies.

Regression analysis of predictors of success rate

Individual patient data was available for 36 patients, reported in three out of the eight studies. Of the variables analyzed, only the type of hydrocephalus on imaging was found to be a significant predictor of outcome. Imaging findings consistent with non-communicating type of hydrocephalus was significantly associated with an odds ratio of 5.90 (95% CI 1.1–32.9, $p = 0.043$) for success.

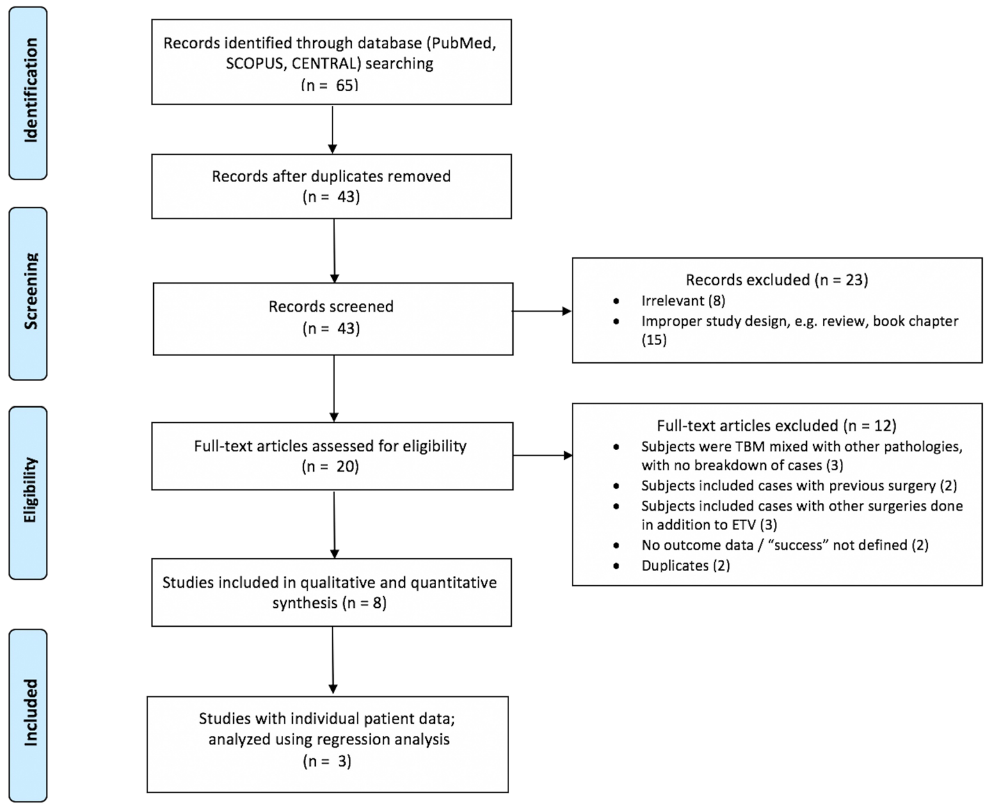

Fig. 1 PRISMA diagram of the systematic review and meta-analysis

Discussion

Our study showed that the pooled success rate for ETV in tuberculous meningitis associated with hydrocephalus was 59%, with an imaging finding of non-communicating type hydrocephalus associated with increased success rate (OR 5.90). Technical failure rate and complication rates were found to be 5% and 19%, respectively, but heterogeneity was moderate for these variables.

This estimate for the success rate did not compare favorably with the rates reported for ETV in non-communicating hydrocephalus which ranges from 75 to 90% [5, 10, 16]. However, it is comparable with the efficacy rates of ETV in communicating hydrocephalus. For instance, Siomin et al. reports success rates of 60.9% and 64.3% for post-hemorrhagic and post-infectious hydrocephalus, respectively, in a multicenter study of 101 patients [25]. Our results are consistent with the fact that in up to 85% of cases, the most common form of hydrocephalus in TBM is of the communicating type [19].

Evidently, the type of hydrocephalus is an important predictor of ETV success. ETV is effective for obstructive hydrocephalus as it provides an alternative route of CSF flow from the third ventricle into the subarachnoid space, while exudates or leptomeningeal scar tissue block the aqueduct or the fourth ventricular outlet in TBM [19]. For communicating hydrocephalus, on the other hand, the mechanisms for its efficacy are less clear. One hypothesis is that ETV allows ventricular CSF to clear thick exudates in the basal cisterns and permeate previously inaccessible areas in the subarachnoid space where CSF absorption may occur [9, 23, 24]. An alternative hypothesis is that by communicating the ventricular and subarachnoid spaces, ETV increases intracranial compliance and reduces systolic pressure transmission into the brain parenchyma, which is hypothesized as the main mechanism of injury in the hydrodynamic concept of communicating hydrocephalus [11, 24].

Presumably due to the relatively small sample size, our individual data patient meta-analysis was not able to detect any other significant predictor of ETV success in TBM. Other studies have reported a trend towards increased success rates in adults (versus pediatrics), lower clinical grade, and better nutritional status [2, 13, 29]. The duration of illness was also reported to directly correlate with success rates, with better outcomes in patients whose illness was diagnosed for longer than 2 months [9, 29]. Yadav attributes this to high incidence of complex hydrocephalus (or mixed communicating and non-communicating type) in the acute phase of the disease [29]. Because the timing of intervention in relation to the onset of illness was not described in many subjects in the included studies, the duration of illness could not be analyzed as a factor in the current meta-analysis. The role of ETV for patients younger than 1 year has been controversial due to initial findings showing decreased efficacy presumed to be

Table 1 Characteristics of studies included in the meta-analysis

Authors, year	Country	Study design	Age range (in years)	Type of HCP[1]	Definition of ETV success	Patients (n)	ETV successes	Technical failures	Complications			Mean F/U
									Mild-moderate	Severe	Fatal	
Goyal et al. 2014 [9]	India	RCT	6 months–16 years	NR	Clinical improvement; and radiologic improvement/stability; and no further CSF diversion surgery	20	10	0	8(5–CSF leak; 3–post-op site swelling)	1 CSF leak w/ men.	1 CSF leak w/ men.	6 m
Yadav et al. 2011 [29]	India	Prospective cohort	6 months–76 years	NC	Clinical improvement	59	34	0	6 (all CSF leak)	0	0	NR
Singh et al. 2008 [24]	India	Prospective cohort	2–25 years	C	Clinical improvement, and radiologic improvement[2]	6	3	0	1	0	0	8 m
Jha et al. 2007 [15]	India	Retrospective cohort	9 months–40 years	B	Clinical improvement, or no further CSF diversion surgery	14	9	1	1 CSF leak	1 IV bleed	0	2.4 m
Figaji et al. 2007 [8]	S. Africa	Retrospective cohort	2–12 years	NC	No further CSF diversion surgery; and improvement in radiographic findings or ICP monitoring	17	7	5	1 CSF leak	1 CSF leak w/ men.	0	NR
Yadav et al. 2006 [27]	India	Prospective cohort	< 1 month	NC	Clinical improvement	6	4	1	NR	NR	NR	NR
Husain et al. 2005 [13]	India	Retrospective cohort	6 months–65 years	B	Clinical improvement; and radiologic improvement/stability; and no further CSF diversion surgery	17	9	2	NR	NR	NR	6.5 m
Singh et al. 2005 [23]	India	Prospective cohort	6 months–32 years	B	Clinical improvement; or no further CSF diversion surgery	35	27	NR	NR	NR	NR	NR

[1] Subjects included either only communicating (C) type hydrocephalus, non-communicating (NC) hydrocephalus, or both (B)

[2] ETV considered successful if post-operative MR ventriculography showed flow of contrast in prepontine and basal cisterns

NR not reported, *CSF* cerebrospinal fluid

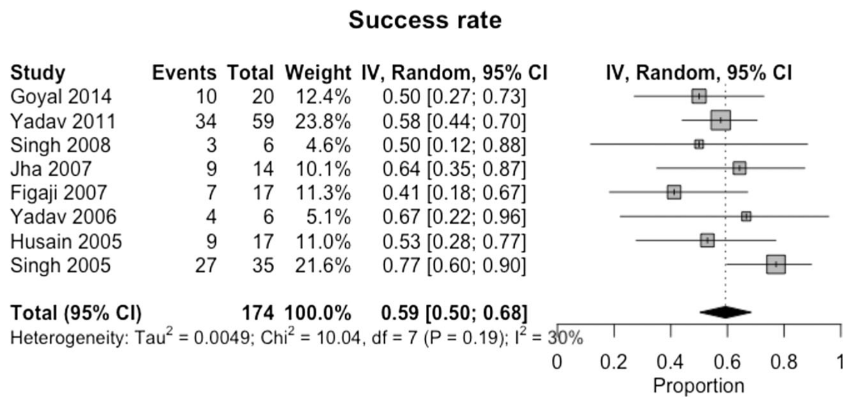

Fig. 2 Random-effects analysis of success rate in 8 studies included in the meta-analysis

due to the immature absorptive capacity of infant brains [4]. In our review, the only study including exclusively infants reported a success rate of 67%, similar to that reported in the rest of the studies [27].

The pooled estimate for technical failure in our study was 5%, comparable with the results of a large meta-analysis of 11,952 ETV cases done for various pathologies [17]. In the latter study, the rate of procedures abandoned due to difficult anatomy, bleeding, or other intraoperative factors was 4.1% ± 4.3% [17]. It is noteworthy that there was considerable heterogeneity in the included studies for this variable ($I^2 = 70$), with rates ranging from 0 to 29%. We posit that possible sources of heterogeneity include surgeon experience and the timing of surgery in relation to the course of illness. ETV has been reported to be more difficult in TBM due to frequent distortion of anatomic landmarks, especially in the acute phase of the disease [7, 15, 19, 29]. Anatomic considerations in TBM include a thick and opaque third ventricular floor, exudates filling the subarachnoid space, and tubercles and granulation tissue in the ependyma which may easily bleed on manipulation [7, 15, 19, 29]. The studies included in this review report several techniques to address these difficulties. Husain et al. and Jha et al. report that their use of the dorsum sella as a readily appreciable and palpable landmark behind the infundibular recess helped in the safe creation of stomas in the often opaque third ventricular floor [13, 15]. Yadav et al. also describe the "water jet dissection technique" in enlarging the stoma in cases of poor visualization in TBM [27–29].

The pooled complication rate in our study was 19%, with considerable heterogeneity in the included studies ($I^2 = 71$). The source of the heterogeneity was a study by Goyal et al. 2014, which was the only study which reported swelling at the post-operative site as a complication. In comparison, the pooled complication rate in a large meta-analysis of ETV cases on different pathologies was 8.9% ± 4.6% [17]. The most common complication in the included studies in our review was CSF leak which was often conservatively managed. These results support the view held by some neurosurgeons that ETV for TBM is generally safe and must be performed as a first-line treatment for all cases, to prevent the complications associated with placement of a permanent shunt.

An important limitation of the current review was the paucity of studies that met the inclusion criteria, limiting the strength of the findings of the meta-analysis. Another limitation is the design and quality of the included studies. Only one study was a randomized controlled trial, assessed to have high risk of performance and detection bias, while none of the observational studies had control groups. There were also differences in the subjects (inclusion of different age groups from different geographical locations), intervention (surgeons presumably had different levels of technical expertise), timing of

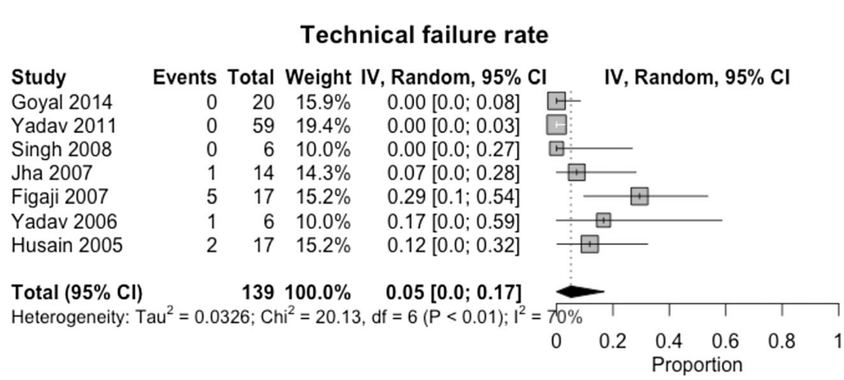

Fig. 3 Random-effects analysis of technical failure rate in 8 studies included in the meta-analysis

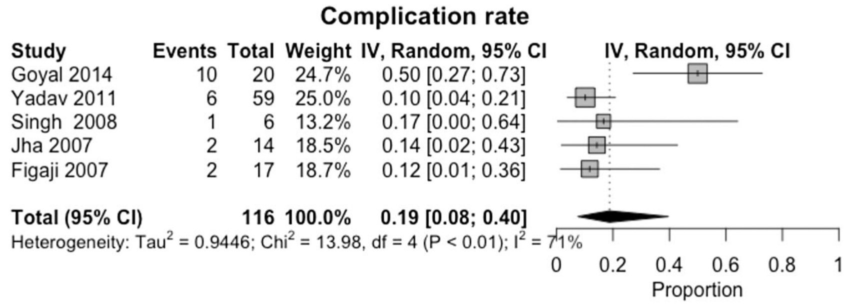

Fig. 4 Random-effects analysis of complication rate in 8 studies included in the meta-analysis

intervention with respect to course of illness (i.e., acute versus chronic TBM), and outcome measures (radiologic versus clinical criterion for success). Because ETV failure is a time-dependent variable, length of follow-up is another potential source of heterogeneity. Results must thus be interpreted cautiously.

Ultimately, the clinically relevant question is whether endoscopic third ventriculostomy is preferable to ventriculoperitoneal shunt insertion, which is the standard of treatment of hydrocephalus associated with TBM. Only one of the included studies in the meta-analysis was such a randomized controlled trial. In this study, of patients with adequate follow-up data to define either success or failure, a successful outcome was noted in 10 out of 20 (50%) who underwent ETV and in 13 out of 17 (76%) who underwent VPS insertion. However, this difference was considered non-significant (p = 0.236) [9]. There was another randomized controlled trial screened in the systematic search, but this was excluded because some patients in the endoscopic third ventriculostomy group also had insertion of an external ventricular drain done, complicating the analysis [1]. The pre-specified exclusion criteria in our study include patients who had another surgical procedure done in addition to ETV. In the published literature evaluating the efficacy of VPS insertion on TBM, "favorable outcome" defined as "excellent, mild, or moderate disability" was reported to be in the range of 55–63% [19]. However, extrapolating this data to our current report on the success of ETV (with a point estimate of around 59%) is difficult owing to the varying definitions of "success" in these studies.

Evidently, there is paucity of data comparing the efficacy and safety of these two interventions in high-quality, randomized, prospective studies. These studies are recommended to definitively define the role of ETV in TBM. In such studies, an important consideration is the determination of outcome data, to include parameters other than success as defined in this study. Clinical and radiographic parameters following successful treatment is known to differ between ETV and VPS, with radiographic size more dramatically responsive to VPS insertion [3]. As such, differences in outcome may be subtle and warrant sensitive, formal neurocognitive testing [3]. In these studies, careful consideration must also be given with regard to timing of intervention, which is an important determinant of success and which was not reported in many of the published studies.

Conclusion

To our knowledge, this is the first meta-analysis on the role of ETV for TBM. ETV was associated with a pooled success rate of 59%, with low heterogeneity of included studies. The only factor predictive of success was non-communicating type of hydrocephalus on imaging. Technical failure and complication failure rates were 5% and 19%, respectively, but heterogeneity was medium-high for these variables. Randomized, prospective studies are needed with VPS insertion used as control to further define the role of ETV in TBM.

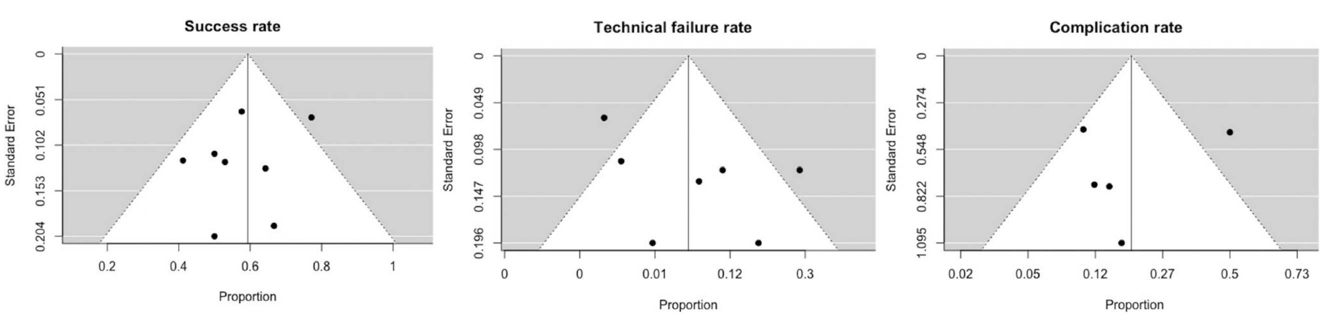

Fig. 5 Funnel plot analysis of success, technical failure, and complication rates in 8 studies included in the meta-analysis

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study is a systematic review and meta-analysis of published studies and does not require ethics approval.

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