# Endoscopic third ventriculostomy versus ventriculoperitoneal shunt in pediatric patients with post-infective hydrocephalus: A meta-analysis of randomized controlled trials

Fenjie Lin MD, Xun Zhang MD, Yinghua Rao MD, Shuchang Zheng MD, Biyan Liang MD, Mingjun Qin MD PhD

Department of Neurosurgery, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, China.

### Abstract

Background: Although studies on the safety and efficacy of endoscopic third ventriculostomy (ETV) and ventriculoperitoneal shunt (VPS) have been conducted, the safety and efficacy for treating postinfective hydrocephalus (PIH) in pediatric patients have not been investigated using meta-analysis and thus remain controversial. Therefore, we conducted a meta-analysis to assess the safety and efficacy of ETV and VPS for PIH treatment and determine whether ETV is more appropriate than VPS for treating PIH in PP. Methods: We searched Pubmed, Embase, Web of Science, and the Cochrane Library databases up to January 2022. The quality of studies was assessed using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials. A fixed-effect model was used for pooling analysis, and heterogeneity was assessed using  $f^2$ . Results: Three randomized controlled trials involving 200 patients out of a total 254 identified studies were included. No significant differences were found between ETV and VPS in postoperative success rate (risk ratio RR: 0.89; 95% confidence interval CI: 0.72-1.10; p = 0.27), postoperative infection rate (RR: 0.68; 95% CI: 0.21-2.22; p =0.52), postoperative blockage rate (RR: 0.90; 95% CI: 0.40–2.00; p = 0.80), complication rates (RR: 1.29; 95% CI: 0.45–3.71; p = 0.63), or mortality (RR: 1.31; 95% CI: 0.47–3.65; p = 0.60). However, patients who underwent VPS showed lower postoperative cerebrospinal fluid leakage than those who underwent ETV (RR: 9.00; 95% CI: 1.18–68.45; p = 0.03).

Conclusions: VPS may be more beneficial for the treatment of PIH in pediatric patients.

*Keywords:* Endoscopic third ventriculostomy, pediatric, post-infective hydrocephalus, ventriculoperitoneal shunt

### INTRODUCTION

Infection, brain tumors, cranioencephalic malformations, and intracranial hemorrhage can cause hydrocephalus.<sup>1,2</sup> Hydrocephalus can lead to increased intracranial pressure, which may lead to headache, vomiting, cranial nerve injury, consciousness disorder, and even death in severe cases, especially in children.<sup>3</sup> Post-infective hydrocephalus (PIH) is the most common form of hydrocephalus worldwide in pediatric patients (PP)<sup>3,4</sup> and is primarily caused by virus, fungi, or bacteria.<sup>5</sup>

cephalus are surgical interventions, such as ventriculoperitoneal shunt (VPS) and endoscopic third ventriculostomy (ETV) with or without choroid plexus cauterization (ETV-CPC). VPS is considered the standard treatment for hydrocephalus over ETV.<sup>6,7</sup> However, recent studies have shown that ETV has a significantly lower risk of surgery-related complications than VPS<sup>8,9</sup>, although Pande *et al.*<sup>10</sup> recommend further research to identify specific patient populations that are better suited for ETV or VPS. There are specific endoscopic challenges that occur as a result of abnormal or indistinct third ventricular

Currently, the main treatments for hydro-

Address correspondence to: Mingjun Qin, M.D., Ph.D., Department of Neurosurgery, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou 510370, China. E-mail: gynksjwk@163.com

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ETV has been widely used to treat hydrocephalus, although primarily in adults. Although ETV has shown encouraging results in older children, outcomes are poorer in younger children.<sup>12,13</sup> Moreover, ETV is not recommended in neonates because of technical difficulties and poor absorption capacity.14 Furthermore, the success rate of ETV for treating PIH is lower than that of VPS.<sup>15,16</sup> Currently, the outcomes following ETV and VPS for the treatment of PIH in pediatric patients remain controversial. Therefore, we conducted a meta-analysis of all RCTs to access the safety and effectiveness of the procedures and determine whether ETV is more appropriate than VPS for treating PIH in PP based on clinical outcomes (postoperative success rate), major complications, and mortality. This meta-analysis will offer guidance for future studies on the treatment of PP with PIH.

### **METHODS**

The methodology of this study followed the Preferred Reporting Items For Systematic reviews and Meta-Analyses guidelines.<sup>17</sup> The protocol was registered on the PROSPERO database (CRD42022311989).

### Search strategy and selection criteria

Four electronic databases were used for the literature search, including Pubmed, Embase, Web of Science, and the Cochrane Library, to search for articles from electronic database inception to January 31, 2022. The following keywords were searched: 'hydrocephalus' and 'ventriculostomy'. We also manually searched the references of the included studies to identify further eligible studies. Two investigators extracted and summarized the search results independently. Disagreements were resolved by consensus.

All articles fulfilled the following inclusion criteria: (1) RCTs comparing VPS with ETV (or ETV-CPC), with quantitative data on the clinical outcomes of interest; (2) all included patients were pediatric (aged  $\leq$  18 years); and (3) all included PP had PIH. Exclusion criteria were as follows: (1) letters, review articles, case reports, or studies in languages other than English; (2) studies that enrolled adults; (3) not an RCT; (4) patients had other types of hydrocephalus; and (5) patients had prior ventriculostomy or shunt surgery. (6) Due to the complex treatment of multiloculated hydrocephalus<sup>18-20</sup>, which was different from the ETV and VPS surgical modalities, it was excluded.

### Data extraction and outcomes

The data were extracted from the eligible studies by two authors independently. The relevant variables extracted included author, year of publication, surgical methodology, number of patients per group, design of the study, etiology of hydrocephalus, age, sex, follow-up time, number of successful cases, mortality rate, and number of complications (e.g., postoperative cerebrospinal fluid (CSF) leakage, postoperative infection, and postoperative blockage, which is regarded as an inadequate stoma in the ETV group or shunt malfunction in the VPS group post-surgery). Surgical procedure success was defined as patients who showed improvements in clinical and radiological profile or did not require a second operation.

### Risk of bias assessment

The quality of the enrolled RCTs was assessed by two authors independently using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials.<sup>21</sup>

### Statistical synthesis and analysis

A dichotomous variable risk ratio (RR) or odds ratio (OR) with a 95% confidence interval (CI) was used to represent the probability of an event occurring. Heterogeneity was assessed using the  $l^2$ -test metric. There was no significant heterogeneity when  $l^2$  was less than 50%<sup>22</sup>, in which case a fixed-effects model was used. Otherwise, a random-effects model was used.<sup>22</sup> The Rev-Man software (version 5.3) was used for all statistical analyses. Statistical significance was set at p < 0.05.

### RESULTS

### Search results

Our search strategy identified 254 potentially relevant studies. Finally, three RCTs<sup>23-25</sup> were included in the meta-analysis (Figure 1).

# Characteristics of the included studies and quality assessment

Table 1 shows the characteristics of the included articles.<sup>23-25</sup> The ETV-CPC surgical method<sup>25</sup>



Figure 1. Flow charts for PRISMA search.

was used in one of the articles. This article was included and considered as ETV because the ETV surgical method played a major role in the surgical procedure. A total of 200 patients were enrolled across the three studies, which comprised 101 patients in the ETV group and 99 patients in the VPS group. All studies<sup>23-25</sup> reported the postoperative success cases (ETV group: 60; VPS

Study	Study design	Number of patients ETV/VPS	Etiology of hydro- cephalus	Age ETV/VPS	Follow-up time	Intervantion/ operation	Female ETV/VPS
Aranha <i>et al</i> . 2018 <sup>20</sup>	RCT	26/26	Tubercular meningitis	NR in the grouping	A minimum of 5 months	ETV/VPS	11/10
Goyal <i>et al</i> . 2014 <sup>21</sup>	RCT	24/24	Tubercular meningitis	4.4±4.60/ 4.31±3.72 (years)	6 months	ETV/VPS	7/7
Kulkarni et al. 2017 <sup>22</sup>	RCT	51/49	NR	2.6- 4.1/ 2.7 - 3.9 (month)	12 months	ETV/VPS	21/18

Table 1. Characteristics of included studies

RCT, randomized controlled trial; ETV, endoscopic third ventriculostomy; VPS, ventriculoperitoneal shunt; NR, not reported

group: 66), the postoperative infection cases (ETV group: 4; VPS group: 6), and the mortality cases (ETV group: 8; VPS group: 6). Two articles<sup>23-24</sup> reported the CSF leakage cases (ETV group: 8; VPS group: 0). Postoperative blockage occurred in 19 patients (ETV group: 9; VPS group: 10) across two studies.<sup>23-24</sup>

According to the Cochrane Handbook for Systematic Reviews of Intervention (version 5.0.2), we assessed the risk of bias in the included studies using the criteria of the risk of bias assessment tool. All studies described the method of randomization. Because patients' family members had the right to know about the operation before the surgery, the blinding of patients, family members, and researchers was impossible across all studies. Therefore, the lack of blinding is unlikely to affect the final results. One<sup>25</sup> of the RCTs was of high quality with a low risk of bias in all domains; however, the quality of the remaining two articles was unclea<sup>23-24</sup> because they lacked information on allocation concealment. The risk of attrition bias was high in the study by Goyal *et al.*<sup>24</sup> because of the population loss. Figure 2 shows the quality assessment of the included studies.

### Postoperative success

For postoperative success rate, all three studies reported a specific number of successful surgeries (126/200, 63%). The pooled data showed that there was no significant difference in the rate of success between the ETV and VPS groups (RR: 0.89; 95% CI: 0.72–1.10; p = 0.27), and there was no significant heterogeneity (P: 0%; p = 0.60; Figure 3).

## Postoperative CSF leakage

Two articles reported complications of



Figure 2. Risk of bias summary.



Figure 3. Forest plot for postoperative success rate.

postoperative CSF leakage. In the ETV group, CSF leakage occurred in eight patients, whereas no patients in the VPS group experienced CSF leakage. After pooling the data, we found that the incidence of CSF leakage in the VPS group was significantly lower than that in the ETV group (RR: 9.00; 95% CI: 1.18–68.45; p = 0.03;  $l^2$ : 0%; Figure 4).

### Postoperative infection

There were four cases of postoperative infection in the ETV group and six cases in the VPS group. There was no significant difference in the incidence of postoperative infection rate between the two groups when data were combined (RR: 0.68; 95% CI: 0.21–2.22; p = 0.52), and there was no significant heterogeneity (*I*<sup>2</sup>: 2%; p =0.36; Figure 5).

### Postoperative blockage

Two of the included RCTs provided data on postoperative blockage. In the ETV group, 18% of patients experienced inadequate stoma or stoma malformation, and 20% of patients in the VPS group experienced shunt malfunction following surgery. The incidence of postoperative blockage was similar across the two groups (RR: 0.90; 95% CI: 0.40–2.00; p = 0.80), and there was no significant heterogeneity ( $I^2$ : 0%; p = 0.86; Figure 6).

### Complication rates in general

The complication rates in general was similar across the two groups (RR: 1.29; 95% CI: 0.45-3.71; p = 0.63), and there was no significant heterogeneity (I<sup>2</sup>: 62%; p = 0.07; Figure 7)

### Mortality

In the ETV and VPS groups, the mortality rates were 7.9% and 6.1%, respectively. After pooling the data, there was no significant difference in overall mortality between the two groups in the treatment of PIH in pediatric patients (RR: 1.31; 95% CI: 0.47–3.65; p = 0.60), and there was no significant heterogeneity ( $I^2$ : 0%; p = 0.83; Figure 8).

### DISCUSSION

A recent meta-analysis revealed a higher incidence of hydrocephalus in the pediatric age group than in adults and older adults.<sup>26</sup> When hydrocephalus is caused by an infective agent, it is defined as PIH and is the most difficult to manage of all the types of hydrocephalus. Both communicating and non-communicating hydrocephalus can be caused by PIH.<sup>16</sup> With recent developments in endoscopy, ETV has a high success rate in the treatment of hydrocephalus.<sup>16,24,27-30</sup> However, Pinto *et al.*<sup>31</sup> reported that VPS is a superior method over ETV because it offers better functional neurological



Figure 4. Forest plot for postoperative CSF leakage rate.

	ETV VPS		5		Risk Ratio	Risk Ratio					
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M	-H, Fixed, 95%	CI	
Aranha 2018	0	26	3	26	53.5%	0.14 [0.01, 2.63]	•				
Goyal 2014	2	24	1	24	15.3%	2.00 [0.19, 20.61]		-			
Kulkarni 2017	2	51	2	49	31.2%	0.96 [0.14, 6.56]					
Total (95% CI)		101		99	100.0%	0.68 [0.21, 2.22]					
Total events	4		6								
Heterogeneity: Chi <sup>2</sup> =	0.01	0.1		10	100						
Test for overall effect: Z = 0.64 (P = 0.52)								0.1	ETV VPS	.0	,00

Figure 5. Forest plot for postoperative infection rate.

	ETV		VPS	VPS		Risk Ratio		Risk Ratio			
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl		M	-H, Fixed, 95%	CI	
Aranha 2018	6	26	7	26	70.0%	0.86 [0.33, 2.21]					
Goyal 2014	3	24	3	24	30.0%	1.00 [0.22, 4.47]		-	-	-	
Total (95% CI)		50		50	100.0%	0.90 [0.40, 2.00]			•		
Total events	9		10								
Heterogeneity: Chi <sup>2</sup> =	0.01	0.1		10	100						
Test for overall effect: Z = 0.26 (P = 0.80)								0.1	ETV VPS	10	100

Figure 6. Forest plot for postoperative blockage rate.

	ETV		VPS	5		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl		M-I	I, Random, 95%	CI	
Aranha 2018	7	26	10	26	42.5%	0.70 [0.32, 1.56]					
Goyal 2014	12	24	4	24	37.9%	3.00 [1.13, 7.99]					
Kulkarni 2017	2	51	2	49	19.6%	0.96 [0.14, 6.56]				_	
Total (95% CI)		101		99	100.0%	1.29 [0.45, 3.71]					
Total events	21		16								
Heterogeneity: Tau <sup>2</sup> =	1, df = 2 (	(P = 0.0	7); <b>I<sup>2</sup> =</b> 62	!%	0.01	0.1	1	10	100		
Test for overall effect:	i3)				0.01	0.1	ETV VPS	10	100		

Figure 7. Forest plot for complication rates in general.



Figure 8. Forest plot for mortality rate.

outcomes 12 months post-surgery for the treatment of idiopathic normal pressure hydrocephalus. Because of the different etiological types of hydrocephalus, for which ETV or VPS may be more appropriate, there is currently no unified standard treatment. Moreover, whether ETV is superior to VPS in the treatment of PIH in PP remains unclear. Due to the complicated treatment of multiloculated hydrocephalus, there was no unified treatment standard at present, which may require repeated revision surgeries, craniotomy or fenestration, or combined with EVT to avoid shunting.<sup>20,32-34</sup> So the treatment of multiloculated hydrocephalus has been temporarily excluded. Thus, we report the first meta-analysis of all ETV- and VPS-related RCTs for the treatment of PIH in PP. The purpose of this meta-analysis was to compare the efficacy and safety of ETV and VPS. Our meta-analysis demonstrated that VPS and ETV are safe and effective for treating PP with PIH, with the possibility that VPS is superior to ETV.

Our meta-analysis showed that surgical success rates were 59.4% in the ETV group and 66.6% in the VPS group after combining data. There was no significant difference in power between the two components. The postoperative success rate of ETV for PP with PIH is similar to that of previous studies (55.9%,<sup>35</sup> 60\%,<sup>30</sup> and 50%<sup>36</sup>). However, Polis *et al.*<sup>15</sup> reported postoperative success rates of 14.7% and 47.77% for ETV and VPS, respectively, which are lower than the rates determined by our meta-analysis. In contrast to the above studies, our study concluded that ETV and VPS are effective for treating PIH as well.

CSF leakage after ETV is a common complication. The incidence of CSF leakage following ETV has been reported to be between 1.6% and 30% in previous studies.<sup>37-40</sup> There were eight patients (1.6%) in the ETV group who had CSF leakage, which was significantly more than the rate of CSF leakage in the VPS group. This may be because the median incision is considered a necessary incision through the catheter from the head to the abdomen during VPS. Early in the course of shunt implantation, intermediate incisions can sometimes crack or the shunt may migrate, which leads to CSF leakage or infection of the shunt system, especially in infant patients. Migration depends on various factors, such as the type of catheter and reservoir used, the fixation technique used, the site and size of the burr hole, and the size of the epidural incision.<sup>41</sup> However, because of the advances in technology, such as the development of a non-intermediate-incision VPS procedure, and the better awareness and prevention of postoperative infection<sup>42,43</sup>, migration can be avoided during the treatment of neonates or infants with PIH. Furthermore, even without improving the VPS procedure, the causes of CSF leakage, such as disconnected parts, broken parts, or the entire shunt ware, rarely occur.41,44 In contrast, after ETV, CSF leakage is more likely because of poorer CSF absorption and the thinning and weakening of the epidural layers of the scalp at the closure, especially in infants.<sup>45</sup> CSF leakage can be a sign of failure of ETV.<sup>46</sup> In our study. the success rate of ETV was slightly lower than that of VPS, and the incidence of CSF leakage was higher following ETV than following VPS. Therefore, we considered that it might indeed be

the image of CSF leakage as well.

Shunt surgery has a higher postoperative infection rate in children, with rates as high as 10%-22% per patient and around 6.0% per procedure.47 Infections, such as meningitis and ventriculitis, have been reported in 1.81% to 6.1% of cases during the immediate postoperative period following ETV surgery.40,48 Such infectious complications are commonly associated with CSF leakage following ETV, whereas in VPS, the use of implantation materials is commonly associated with infections. In the study of Goyal et al.<sup>24</sup>, CSF leakage was reported in seven cases in the ETV group; 14.3% of patients with CSF leakage developed meningitis, of whom one died. Therefore, attention must be paid to the postoperative complications of CSF leakage and infections. In our meta-analysis, the incidence of infection following VPS did not significantly differ from that following ETV (6.1% vs. 4.0%)after pooling data, and the rate of infection was similar to those reported in the above studies.

In addition, nine cases in the ETV group and 10 cases in the VPS group had postoperative blockage, although this difference was not significant.

Although in our analysis, the incidence of CSF leakage complications was higher in the ETV group than that in the VPS group. However, the comparison between the two methods seems to be flawed in terms of CSF leakage. The incidence of ETV combined with CSF leakage is high in literature reports (between 1.6% and 30%), while the incidence of CSF leakage in VPS is only possible when the technique is defective. Therefore, we believe that this simple statistical comparison may be biased, and further comparison of more sample sizes may be needed to assess whether there is a significant difference in the incidence of CSF leakage between the two groups. For this, we also statistically analyzed the complication rates in general of the two groups. Although the complication rates of the VPS group was slightly lower than that of the ETV group, there was no statistical difference between the two groups. This is similar to the previous study<sup>10</sup> on the complication rates of ETV and VPS subgrouped by RCTs.

Texakalidis *et al.*<sup>8</sup> performed a metaanalysis comparing ETV and VPS for pediatric hydrocephalus, which included 8419 patients (not specifically with PIH), and reported all-cause mortality rates of 4.5% and 8.5% for ETV and VPS, respectively. In our study, the mortality rate of ETV (7.9%) was higher than that in the above study. This may be because we included only RCTs, which limited the sample size. In addition, PIH is the most difficult hydrocephalus type to manage, and the study by Texakalidis *et al*. did not specifically explore PIH. However, it is notable that the mortality rate following VPS (6.1%) in our study was lower than that in the above study. This may indicate that VPS is more advantageous in treating PIH. However, we did not find a statistical difference between ETV and VPS for mortality rate.

There are several limitations to this metaanalysis: 1) only three RCTs with small sample sizes were included in our analysis, which may affect the generalizability of the results, and additional RCTs using large sample sizes are needed for validation; 2) although heterogeneity was not significant, different etiologies of PIH in PP may have introduced some bias; 3) in the combined analysis, ETV and ETV-CPC were combined, which may have biased the results, and further subgroup analyses are needed in future studies. 4)Due to the short follow-up period, we could not know the long-term prognosis of the two surgical methods. Despite these limitations, our meta-analysis was logically and rigorously conducted and may provide a valuable reference for future research.

In conclusion, our meta-analysis showed that the incidence of CSF leakage was higher following ETV than following VPS, which may have an impact on surgical success. However, there were no significant differences between VPS and ETV in postoperative infection rate, postoperative blockage rate, complication rates in general, or mortality rate. Therefore, VPS may be more beneficial for PP with PIH. However, our findings require verification in further RCTs using large sample sizes.

### DISCLOSURE

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