Long-term outcomes of endoscopic third ventriculostomy in adults

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Highlights

• ETV has good long term efficacy in adults with hydrocephalus, with a low risk of complications (6%).
• Patients with a prior shunt have a higher risk of ETV failure.
• ETV is a first-line treatment in patients with tectal gliomas.
• Although most ETV failures occur within 2 years, long-term failures can also occur and recurrent symptoms should prompt neurosurgical workup.
Abstract

Objectives. To describe long-term outcomes of endoscopic third ventriculostomy (ETV) in adults with hydrocephalus.

Methods. Single-institution retrospective review of adults treated with an ETV between 1998-2006. Patient demographics, treatment and follow-up data was collected. Patients were divided into two groups: primary ETV for previously untreated or newly diagnosed hydrocephalus; and secondary ETV in patients with prior shunts presenting with shunt malfunction. ETV outcome was deemed as successful if patients remained shunt-free after ETV. Multivariate analysis was performed using Cox regression.

Results. 190 patients were included. Median age: 43 (range 16-79) years. Median follow-up period: 112 (range 1-190) months. The primary and secondary ETV groups contained 129 and 61 patients, respectively. Operative complications occurred in 11 patients (6%). A successful outcome was obtained in 139 patients (73%). ETV failure occurred in 51 patients and the median time to failure was 2 (range 0-124) months. Although the majority (86%) of ETV failures occurred within 2 years postoperatively, failure was noted in 3 cases between 5-10 years after intervention, including one patient who at 124 months follow-up. In multivariate analysis, only previous shunt was found to influence outcomes (p = 0.021), with a shorter ETV survival noted in patients with a prior shunt. Age, indication and ETV success score, did not influence outcome.

Conclusions. ETV is a safe procedure with excellent rates of long-term efficacy. However, late failure can occur and patients should be instructed to seek medical advice if symptoms reoccur. Prior shunt is associated with a higher ETV failure rate.

Key words
Hydrocephalus; endoscopic third ventriculostomy; shunt; long-term outcomes.

Running title
Long-term ETV outcomes in adults

Abbreviations
ETV = endoscopic third ventriculostomy; LOVA = long-standing overt ventriculomegaly in adults.
Introduction

Endoscopic third ventriculostomy (ETV) was first performed by Mixter in 1923 and has since become an established treatment modality for obstructive hydrocephalus in children.\(^1\) However, its efficacy depends on several factors including indication, whether patients have previously received a shunt and patient age. Age is a particularly important factor as rates of CSF reabsorption appear to decrease with increasing age, such that the efficacy of ventriculostomy, which diverts CSF to the subarachnoid space through a fistula in the third ventricle floor, may decrease with age.\(^2\)-\(^4\) However, studies reporting long-term efficacy in adults are generally sparse and limited by sample size. We have previously reported our institutional experience with ETV in adults.\(^5\) In this study, we report our updated experience with longer-term outcomes.

Methods

Study population

The institutional review board approved this study. Adult (\(\geq 16\) years) patients who underwent an ETV at our institution (The Walton Centre Foundation Trust, Liverpool, UK) between April 1998 to August 2007 were included for case-notes review. Data was collected pertaining to patient demographics, cause of hydrocephalus, ETV indication, operative complications and follow-up treatment. The aetiology of hydrocephalus was classified as aqueduct stenosis, long-standing overt ventriculomegaly in adults (LOVA), tumour, Chiari malformation and others. The ETV success score was also calculated for each patient as previously described.\(^6\) Patients were divided into two ETV groups: primary ETV for previously untreated or newly diagnosed hydrocephalus; and secondary ETV in patients with prior shunts presenting with shunt malfunction.

Procedure

The operative technique has been previously described.\(^5,\)\(^7\) Briefly, patients were placed supine, with head flexed at 10°. A right precoronal burr hole was created 3cm from the midline. An introducing catheter was inserted into the right lateral ventricle to a depth of 4-5 cm, and the inner sleeve was withdrawn. A variety of endoscopes were used including flexible and rigid instruments. The endoscope was inserted and guided through the foramen of Monro into the third ventricle. A light-touch balloon (NMT Neurosciences) was used to fenestrate the floor midway between the infundibulum and mammillary bodies. Appearances of the third ventricle are demonstrated in Fig. 1. The fenestration was entered to inspect the prepontine space, to confirm a clear path to the subarachnoid space. If multiple membranes were encountered, these were also fenestrated. The cortical hole left by the endoscope was plugged with thick Spongostan (Johnson & Johnson) to avoid CSF leakage into the subdural space and the wound was closed. In cases of shunt malfunction, the shunt was removed in its entirety unless it was deemed to be so old or embedded that it was dangerous to do so. Other ventricular access devices (e.g. EVD or CSF reservoirs) were not routinely inserted at the time of ETV.

Statistics and outcomes

Statistics were performed using SPSS version 21 (SPSS Inc., Chicago, USA). ETV outcome was deemed as successful if patients remained shunt-independent after ETV placement. ETV survival was calculated in
months from the date of surgery to the date of shunt placement, or censored at the date of last follow-up if the patient remained shunt-independent. Survival analysis was used to determine the effect of the following on ETV success: age (≤ vs. >median age), presence of previous shunt, indication and ETV success score (≥80 vs. <80). Univariate analysis was performed using Kaplan Meier survival curves and the log-rank test. Multivariate analysis was performed using a forward stepwise cox regression model, including variables where p<0.1 in univariate analysis.

Results

Patient characteristics
190 patients underwent an ETV procedure during the study period. The median patient age was 43 years (range 16-79 years) and the median follow-up period was 112 (range 1-190) months. The primary ETV group contained 129 patients and the secondary ETV group contained 61 patients. The primary ETV group was older on average (mean age 45 vs. 36 years, independent t-test, t = 3.692, p < 0.001). Patients in the secondary group had failure of ventriculoperitoneal (n = 56, 92%) or ventriculoatrial (n = 5, 8%) shunts.

Complications and mortality
Operative complications occurred in 11 (6%) patients, including three cases of procedure abandonment due to abnormal anatomy (n = 2) or profuse bleeding (n = 1). Other complications included minor intraoperative haemorrhage (n = 2), CSF leak (n = 2), asymptomatic subdural haematomas (n = 2) and transient abducens palsy (n = 2). None of these 11 patients had early (<1 month) postoperative mortality. There were 42 deaths during the follow-up period and the majority were in the primary ETV group (n = 34, 81%). Cause of death data could not be obtained. Overall mortality rates were 26% and 13%, in the primary and secondary ETV groups, respectively.

Repeat ETV procedures
15 patients required either one or more repeat ETV procedures. All patients had evidence of complete or partial closure of the ventriculostomy site on dynamic CSF-MRI flow studies. The commonest underlying pathology in patients undergoing a repeat procedure included tumour/colloid cyst (n = 5) and LOVA (n = 4). The proportion of patients undergoing a repeat procedure was similar between the primary and secondary groups (6% vs. 12%, Fisher’s Exact, p = 0.251). In the repeat ETV cohort, 9 patients (60%) remain shunt-free. A repeat procedure was performed at a median of 39 (range 1-163) months after the first procedure. Two patients required a second repeat procedure at range of 15-19 months after the first and one remains shunt-free.

Shunt-independence
A successful ETV outcome was obtained in 139 patients (73%). The ETV success rate in each group is shown in Table 1. The primary ETV group had a higher rate of ETV success (Fisher’s exact, p = 0.005). ETV survival was longer in the primary ETV group (log-rank = 8.444, p = 0.004) (Table 3 and Fig. 2A).
ETV failure occurred in 51 patients and the median time to ETV failure was 2 (range 0-124) months. The majority of failures (44/51, 86%) occurred within the first two years of operation. There were 7 cases of failure beyond this timeframe, including 4 between 2-5 years postoperatively and 3 between 5-10 years postoperatively. The 5-10 year group included one patient who re-presented with symptoms of hydrocephalus after 124 months (10 years) follow-up. The time to ETV failure was not significantly different between the groups (11 vs. 13, independent t-test, t = 0.264, p = 0.793). In the cohort of patients with an ETV survival time of 2 years or more, there were only 7 failures out of 118 patients (Fig. 2B). Most of these failures occurred in the secondary ETV group (5 vs. 2, log-rank = 5.230, p = 0.022).

Aetiology
Rates of shunt-independence within each ETV group, stratified by cause, are shown in Table 2 and illustrated in Fig. 3. The most common primary and secondary indications for an ETV were tumour and shunt blockage, in 51% and 85% of patients, respectively. In the primary ETV group, success rates by diagnosis were as follows: aqueduct stenosis 89%, LOV A 83%, chiari malformations 89%, tumours 76%. Other primary causes had an overall success rate of 82%. In the secondary ETV group, success rates by underlying indication were 62% for mechanical shunt blockage and 44% for shunt infection.

Outcomes
In univariate analysis, younger age (log-rank = 4.091, p = 0.043), previous shunt (log-rank = 8.444, p = 0.004) and post-infectious aetiology were associated with a shorter duration of ETV survival. Other factors did not influence outcome: ETV success score (log-rank = 0.075, p = 0.784), or indications for ETV such as tumour (log-rank = 0.217, p = 0.641), aqueduct stenosis or LOVA (log-rank = 0.888, p = 0.346), chiari and spina bifida (log-rank = 0.539, p = 0.463) and post-haemorrhagic hydrocephalus (log-rank = 0.186, p = 0.666). For multivariate cox regression, post-infectious aetiology was excluded due to significant bias of group sizes. At the multivariate level, previous shunt (p = 0.021; HR = 1.946, 95% CI 1.108 - 3.419), but not age (p = 0.146; HR = 0.646, 95% CI 0.358 - 1.165), was found to influence outcome.

Discussion
In this study, we have updated our ETV experience and presented outcomes after long-term follow-up. In our cohort of patients with hydrocephalus of various aetiologies, an ETV was used as first-line treatment in most (68%) cases, with only a minority (32%) receiving it after shunt-failure. After long-term follow-up (median 112 months), a successful ETV outcome was obtained in 139 patients (73%), which is a 5% drop compared to our previous report. Indeed, although the vast majority (86%) of ETV failures occurred within 2-years of the procedure, late failures (>5 years) were noted in a handful (three) of cases, including one that occurred up to 10 years postoperatively. Finally, using multivariate analysis, we found that previous shunt was the only factor that predicted outcome in adults with ETV.

Long-term efficacy
Studies that have reported outcomes with ETV in adults after at least 2-years follow-up are presented in Table 4. The reported efficacy varies widely between 55-100%. However, this is probably due to
differences in inclusion criteria as the efficacy of ETV is also dependent on indication. The studies by Buxton et al. and Santamarta et al. presented outcomes in unselected adults with hydrocephalus, mostly caused by aqueduct stenosis or neoplasm. The proportion of patients remaining shunt-free were marginally lower in the study employing longer follow-up (73% vs. 80%), which supports our findings of late ETV failures.\textsuperscript{9, 12} It is well established that most ETV failures occur early, if at all.\textsuperscript{9, 12, 20, 21} As with all patients with hydrocephalus, long-term follow-up is often required either through annual clinic review or an open access emergency hydrocephalus clinic. In view of our findings, a strategy to discharge patients after 2 years of follow-up is feasible, but patients should be warned about the possibility of late failure and given rapid access to the hydrocephalus service in the event of symptom recurrence. Acute failure can occur and is recognized as potentially fatal.\textsuperscript{22}

A recently published study by Grand et al. included 243 patients in whom ETV was possible. After a mean follow-up period of 6 years, the authors reported ETV failure in 66 patients, of which 36 required a shunt procedure (85% shunt-free). However, it should be noted that there was a relatively high rate of parent refusal to further treatment and/or loss to follow-up. This was the case in 18 of the remaining 30 patients with ETV failure, such that the actual rate of ETV success was probably closer to about 78%.\textsuperscript{19} Our study further adds to the literature by presenting outcomes after a longer follow-up period and evaluating prognostic factors associated with ETV success.

In cases of ETV failure, where symptoms re-occur, CSF flow studies are performed at our institution to guide management decisions. A further attempt at ventriculostomy is undertaken only where there is demonstrable impairment of flow through the fenestration site. In the present study, around one third of patients treated with an ETV required either an immediate shunt or redo procedure. Of the patients undergoing a redo procedure, 9 out of 15 (60%) remain shunt-free. Other studies that have presented results of repeat ETV procedures have found an even higher rate of success between 83-96% and a repeat procedure is therefore recommended where indicated.\textsuperscript{23, 24}

Complications
Intra and post-operative complications were noted in 6% of patients in this study. This is similar to other reports, though higher rates (>10%) of complications have also been reported using the same surgical technique.\textsuperscript{9, 20, 25} The main intraoperative complication is haemorrhage, that can be severe and result in procedure abandonment. Recently, some authors have also reported outcomes with laser-assisted ETV, though complication rates appear to be higher than studies employing conventional techniques, at around 10%.\textsuperscript{26, 27} Although not a complication per se, a minority of patients also harbour anatomical variants of the third ventricle floor, which preclude successful fenestration. Such patients are encountered very rarely however and we noted only two during the study period.

Tumours
Pineal and tectal tumours are especially prone to causing obstructive hydrocephalus and an endoscopic technique allows for concomitant tumour sampling and treatment of hydrocephalus. ETV is desirable for treatment of hydrocephalus given that most of these tumours are likely to be low-grade gliomas and non-
curable, such that potential complications from shunt placement are difficult to justify. In the present study, ETV was successful in ~75-80% of tectal and pineal lesions, which represents an excellent rate of long-term control. The present study also builds on our previous work on tectal gliomas, recommending ETV as a primary treatment modality for these tumours. Studies have also presented favourable outcomes with pineal tumours. Chibbaro et al. presented their experience with ETV for posterior third ventricle and pineal region tumours, and reported that 100% of patients were shunt-free after 39 months mean follow-up. Other studies have found similar results. However, patients with caudal brainstem tumours may not do so favourably. Indeed, patients with cerebello-pontine angle tumours had a particularly high rate of ETV failure (40%) in the present study.

Aqueduct stenosis and LOVA

Aqueduct stenosis can occur in the primary form, where clinical features of hydrocephalus develop acutely in previously healthy adults. Alternatively, it can occur in children and adolescents, with insidious ventriculomegaly that usually manifests in adulthood. This latter syndrome (LOVA), is usually asymptomatic as a result of compensated CSF flow dynamics, though symptoms can develop. Long-term control of hydrocephalus induced by these pathologies was 80-90% in the present study and compares well to other studies. However, considerably lower rates of efficacy have also been reported. Tissel et al. deemed 9 out of 18 patients who underwent an ETV for aqueduct stenosis, to have an unsatisfactory outcome after 37 months mean follow-up. However, only 7 patients were further investigated and offered shunt placement, including one patient with blocked convexity CSF flow, despite slight clinical improvement and decreased ventricular size. The authors did not clarify why they investigated and offered further treatment to only a proportion of patients they deemed to have an unsatisfactory outcome. This limitation only partially explains their relatively poor outcomes, however.

Other primary indications

Other patient groups that benefited from primary ETV therapy included patients with Chiari type 1 malformations. Our findings are again supported by other studies presenting outcomes after medium to long-term follow-up with these patients. In one study, 5 out of 5 patients with Chiari-1 malformations remained shunt-free after 50 months mean follow-up, including one patient who underwent a successful repeat procedure. Complications were relatively high due to one transient wound-infection in the study. Our study was not sufficiently powered to convey data on the efficacy of ETV for indications such as NPH, though excellent medium to long-term outcomes have been reported. In one study, 86% of patients with NPH remained shunt-free during 78 months mean follow-up, though a significant proportion (>50%) of patients with unsatisfactory outcome refused further surgery.

ETV for shunt-failure (secondary ETV)

The efficacy of ETV after shunt-failure was 59% in the present study, in which the majority of patients were offered ETV for mechanical shunt blockage. Furthermore, previous shunt was the only factor that influence outcome in this cohort of adults with ETV. Other studies have also reported a similarly low efficacy of ETV after shunt failure. Kulkarni et al. also recognised this negative prognostic factor in their description of the ETV success score, which awards a higher probability of success to patients who are shunt-naive at

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presentation. The overall score itself was not found to influence survival in this cohort, and this is to be expected as it was primarily intended for paediatric patients. It is clear that patients with a prior shunt represent a select cohort that is more difficult to treat. Despite the relatively lower rate of long-term efficacy, patients presenting with shunt failure should be considered for ETV where appropriate, with vigilant clinical follow-up postoperatively.

Limitations

Limitations of the present study include its retrospective design and small patient numbers in some subcategories. Indeed, despite the current interest surrounding ETV for NPH, this could not be assessed with certainty due to limitations of sample size. In addition, we did not report on quality of life or symptom related outcomes, though arguably patients would be expected to re-present to our regional referral centre in the setting of recurrent symptoms. Our definition of ETV failure was based on symptomatic relapsed hydrocephalus that required a shunt. Other patient groups that could have arguably "failed" included patients who were successfully treated with a redo ETV procedure and remained shunt-free, which we regarded as a successful outcome. This approach could also have missed patients with asymptomatic, compensated hydrocephalus post-operatively.

Conclusion

In this study, we updated our ETV experience after long-term follow-up (median 112 months) in a cohort of 190 adult patients with hydrocephalus of multiple aetiologies. ETV remains a safe (6% complication rate) and effective (73% shunt-free) procedure for obstructive hydrocephalus, with greater success rate when performed as a first-line intervention rather than after shunt failure. A successful ETV outcome was obtained in 139 patients (73%), which is lower than our previous report and highlights the occurrence of late failures. Although the majority (86%) of ETV failures occurred within 2 years of the procedure, late failures (>5 years) were noted in three cases, including one patient who failed after 124 months follow-up. Although a strategy to discharge patients after 2 years of follow-up is feasible, patients should be warned about the possibility of late failure and given rapid access to the hydrocephalus service in the event of symptom recurrence.

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Disclosures

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


Table and Figure legends

Table 1. Overall ETV success rate in primary and secondary groups.

Table 2. ETV success rates by subcategories of primary and secondary groups.

Table 3. Actuarial rates of ETV survival. The proportion of patients remaining shunt-free was consistently higher in the primary ETV group.

Table 4. ETV success rates in contemporary literature. Note that this table only includes those studies reporting after a follow-up of at least 2 years. AS = aqueduct stenosis; NPH = normal pressure hydrocephalus.

Figure 1. T2 sagittal MRI showing third ventricle anatomy, in (A) normal; (B) hydrocephalus pre-surgery; and (C) hydrocephalus post-ETV. Open arrowheads show the tectal plate and aqueduct below. Note in (B) the aqueduct is expanded indicating high pressure and in (C) the aqueduct is smaller following the ETV. Closed arrowhead shows flow (low signal intensity) through the ventriculostomy in the third ventricle floor.

Figure 2. ETV survival by group. The ETV survival time was longer in the primary ETV group (A) in entire cohort (p = 0.004) and, (B) in the cohort of patients with an ETV survival time of >24 months (p = 0.022).

Figure 3. ETV survival by aetiology. (A) In all patients. (B) In the primary ETV group. (C) In the secondary ETV group.
### Table 1

<table>
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<th>Primary (%)</th>
<th>Secondary (%)</th>
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<td>36 (59%)</td>
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<td>Failure</td>
<td>26 (20%)</td>
<td>25 (41%)</td>
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<td>Total</td>
<td>129</td>
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### Table 2

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<td>Secondary</td>
<td>Primary</td>
<td>Secondary</td>
</tr>
<tr>
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<td>n</td>
<td>Success rate, n (%)</td>
<td>n</td>
<td>Success rate, n (%)</td>
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<td>-</td>
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<td>9</td>
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### Table 3

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<th>Proportion remaining shunt-free</th>
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### Table 4

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<th>Age, years (range)</th>
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<th>Shunt-free (%)</th>
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<td>45 (±16)</td>
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<td>7</td>
<td>72 (68-72)</td>
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<td>NPH</td>
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<td>Gangemi 2008 [13]</td>
<td>110</td>
<td>67 (51-83)</td>
<td>78 (24-144)</td>
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<td>86%</td>
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<td>Decq 2001 [10]</td>
<td>5</td>
<td>29.6 (18-46)</td>
<td>50.3 (14-109)</td>
<td>20%</td>
<td>100%</td>
<td>Chiari-1</td>
</tr>
<tr>
<td>Buxton 2001 [9]</td>
<td>63</td>
<td>32 (17-77)</td>
<td>37 (0-84)</td>
<td>17.5%</td>
<td>80%</td>
<td>Unselected</td>
</tr>
</tbody>
</table>
Figure 1.
T2 sagittal MRI showing third ventricle anatomy, in (A) normal; (B) hydrocephalus pre-surgery; and (C) hydrocephalus post-ETV. Open arrowheads show the tectal plate and aqueduct below. Note in (B) the aqueduct is expanded indicating high pressure and in (C) the aqueduct is smaller following the ETV. Closed arrowhead shows flow (low signal intensity) through the ventriculostomy in the third ventricle floor.