Improving outcomes in pediatric endoscopic third ventriculostomy through outcome analysis and surgeon training
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Chapter 2

An external validation of the ETVSS for both short-term and long-term predictive adequacy in 104 pediatric patients

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Abstract

Purpose
This study aims to provide external validation of the “Endoscopic Third Ventriculostomy Success Score (ETVSS)” for both short-term and long-term predictive adequacy.

Methods
Between 1998 and 2007, we collected clinical follow-up data (after 6 and 36 months) of all 104 hydrocephalic children (<18 years of age) treated by endoscopic third ventriculostomy (ETV) in our hospital. Predictive adequacy of ETVSS for 6- and 36-month periods was tested by means of an unpaired t test, Hosmer–Lemeshow “goodness-of-fit” test, and area under the receiver operating characteristic curve.

Results
Mean follow-up was 73.4 months. For both the short-term (6 months) and the long-term (36 months) periods, the mean predicted probability of ETV for the patients with successful ETV treatment was significantly higher than in the patients with failed ETV treatment. The areas under the curve for the short- and long-term periods were, respectively, 0.82 (95 % CI 0.71–0.92) and 0.73 (95 % CI 0.62–0.84). For patients with moderate ETVSS (50–70), the median age at first ETV was significantly higher for patients with successful ETV for both short- and long-term periods.

Conclusion
In hydrocephalic children, the ETVSS is a useful tool for prediction of outcome after ETV treatment. The ETVSS is more adequate in predicting short-term than long-term success. In our population, it is suggested that success rate for patients with moderate ETVSS could be improved if more weight is attributed to age at first ETV.
Introduction

Endoscopic third ventriculostomy (ETV) is a commonly used and accepted method for treatment of obstructive hydrocephalus. A major advantage of ETV in relation with ventriculoperitoneal shunting (VP shunt) is that the first procedure does not leave a foreign body. There is no consensus regarding the role of ETV in young pediatric patients. Hopefully, the International Infant Hydrocephalus Study will provide a more definite answer in the future. Meanwhile, the ETV Success Score (ETVSS) may be applied to predict whether an ETV is likely to be successful. The ETVSS is derived from three variables: patient age, etiology of hydrocephalus, and the presence of previous treatment with VP shunt. After internal and external validation, the ETVSS has been applied in many studies, revealing a good short-term prediction. This study provides external validation of the ETVSS at the 6-month follow-up. Ultimately, it is essential that the treatment continues to be successful in the long-term and therefore we perform an additional test of the long-term (36 months) adequacy of the ETVSS. A retrospective cohort study is presented of a series of children (n=104) under 18 years of age who all underwent ETV as treatment for hydrocephalus at the University Medical Centre Groningen (UMCG).

Methods

Study design

Between 1998 and 2007, we retrospectively collected all clinical data of children who received an ETV at the UMCG (Fig. 1). Ten patients died before the 6-month follow-up criterion was met; seven patients died of tumor-related causes, three patients died of other causes (Walker–Warburg syndrome, congenital heart disease, and respiratory failure due to bacterial pneumonia), and none died of causes related to hydrocephalus. All ETV procedures were performed in accordance with national guidelines, i.e., either by a neurosurgeon or a resident under direct supervision of a neurosurgeon. ETV failure was diagnosed by a clinician, with additional radiologic information.
From patient records, we collected data regarding basic patient characteristics, etiology of hydrocephalus, age at first ETV treatment, primary ETV, or secondary ETV (after previous VP shunt treatment). ETV failure was indirectly determined by additional HC requirement or death. Late ETV failure is defined as failure of ETV between 6 and 36 months. Re-ETV is defined as a repeated ETV procedure after failure of the initial ETV.

According to Naftel et al., we apply the term “salvage” ETV when the ETV decision is based upon multiple shunt failures and/or poor CSF absorption, instead of straight ETV criteria. We report all ETV treatments fitting “salvage” category of both initial ETV and re-ETV treatments. No additional analysis was performed on the “salvage” category.

In all patients, MRI scans were made pre-operatively in order to contribute to the definition of the etiology of the hydrocephalus. The following categories were identified in concordance with the original paper on ETVSS: aqueductal stenosis, post-infectious, myelomeningocele, post-intraventricular hemorrhage, tectal tumor, other brain tumor (non-tectal), and other causes. For each patient, the ETVSS is subsequently calculated by combining age, etiology, and previous shunt score (Table 1). The calculated scores show a range...
Table 1. Calculation of the ETVSS (after Kulkarni et al.17)

<table>
<thead>
<tr>
<th>Score</th>
<th>Age</th>
<th>Etiology</th>
<th>Previous Shunt</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&lt; 1 month</td>
<td>Post-infectious</td>
<td>Previous shunt</td>
</tr>
<tr>
<td>10</td>
<td>1 month to &lt; 6 months</td>
<td>Myelomeningocele, intra-ventricular hemorrhage, non-tectal brain tumor</td>
<td>No previous shunt</td>
</tr>
<tr>
<td>20</td>
<td>6 months to &lt; 1 year</td>
<td>Aqueductal stenosis, tectal tumor, other etiology</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>1 year to &lt; 10 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>≥ 10 years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

from 0 to 90 related to predicted success rates after 6 months. For example, for a 2-month-old child with an aqueductal stenosis in absence of previous CSF shunt treatment, a total score of 50 would be applicable. This score is composed of 10 points for age, 30 points for etiology of hydrocephalus, and 10 points for “previous shunt.” A patient with ETVSS of 50 is postulated to have a 50% chance of successful ETV treatment for a period of 6 months.

Statistical analysis
We performed data analysis with the statistical package SPSS for Windows (version 20). Baseline characteristics are reported as mean with SD or as numbers with corresponding percentages. If variables were not normally distributed, values are reported as median with interquartile range (IQR). The duration of follow-up after surgery was calculated till the date of subsequent hydrocephalus treatment or date of death, or was ceased at the last date at which the patient was seen at the treating center and known to be well.

The cohort was stratified based on ETVSS in three different categories: low ETVSS (≤40), moderate ETVSS (50–70), and high ETVSS (≥80). Kaplan–Meier curves indicated the shunt failure-free survival rate for the different strata. We calculated the hazard ratios for ETV failure for the different ETVSS strata by Cox regression analysis. Differences in mean ETVSS and median age in months at ETV treatment between patients with early ETV failure and late ETV failure were analyzed by, respectively, the unpaired t test and Mann–Whitney U test.

We compared differences in median age at ETV treatment between patients with successful and failed ETV in the moderate ETVSS group by Mann–Whitney U test. Between-group comparisons of nominal or ordinal variables were performed
for the moderate ETVSS group by Chisquare and/or by Fisher’s exact test. We considered p values <0.05 as statistically significant.

We determined external validity of the ETVSS model by Kulkarni et al.\textsuperscript{17} over a short-term (6 months) and a long-term (36 months) follow-up period. We compared the predicted probability of ETV success between children with successful and failed ETV treatment by an unpaired t test. Performance of the predictive model was subsequently tested by the Hosmer–Lemeshow “goodness-of-fit” statistic; a significant p value rejects the null hypothesis that the model fits the data well. Model discrimination was quantified by the area under the receiver operating characteristic (ROC) curve.

**Results**

**Patient characteristics**

Patient characteristics of 104 children are presented in Table 2. The mean follow-up period was 73.4 months (SD, 38.7). The first ETV was performed at a median age of 67.7 months (IQR, 3.1–117.5). Of all ETV treatments performed in the inclusion period, seven patients qualified for the “salvage” category; in three of these patients, ETV appeared successful.

**Short-term predictive adequacy (6 months)**

Mean ETVSS was 66.2 (SD, 17.0), and actual overall ETV success rate after 6 months was 70.2 %. The remaining 31 (29.8 %) patients received subsequent treatment, consisting of VP shunt implantation or revision (29 children; 93.5 %), or a repeated ETV (2 children; 6.5 %).

The mean predicted probability of ETV success was significantly higher in children with successful ETV than ETV failure [0.72 (SD, 0.13) vs. 0.52 (SD, 0.1), with a mean difference of 0.21 (95 % CI 0.15–0.27; p<.001)]. The Hosmer–Lemeshow statistic revealed an adequate model fit (p=.10). The area under the curve is 0.82 (95 % CI 0.71–0.92).

**Long-term predictive adequacy (36 months)**

In 84 of 104 (80.8 %) patients, a follow-up period of at least 36 months was
available. The mean ETVSS for this group was 66.0 (SD, 16.6). The actual overall ETV success rate after 36 months in this group was 48.8 % (n=41). Within the extended follow-up period of 36 months, a total of 43 (51.2 %) patients underwent subsequent treatment, of which 27 (62.8 %) patients received a VP shunt (or revision of a present VP shunt system) and 16 (37.2 %) received a re-ETV. Twenty-seven of 43 (62.8 %) patients had early failure. The mean predicted probability of ETV success was significantly higher in children with successful than failed ETVs [0.73 (SD, 0.14) vs. 0.59 (SD, 0.17), mean difference of 0.14 (95 % CI 0.071–0.20; p<.001)]. The Hosmer–Lemeshow revealed an adequate model fit (p=.77), and the area under the curve is 0.73 (95 % CI 0.62–0.84).
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ETVSS strata
According to Kulkarni et al., we characterized ETVSS outcomes as low, moderate, and high in 17, 47, and 40 children, respectively. In Tables 3 and 4, mean ETVSS and the actual success rate within these ETVSS strata are displayed for, respectively, the 6- and 36-month follow-up period. The ETVSS and the actual success rate for the different strata for the children under the age of 2 years are shown in Table 5. Patient characteristics of the moderate ETVSS group are indicated in Table 6.

Comparing low with high ETVSS reveals a 5.5-fold chance of ETV failure within the next 36 months (95 % CI 2.5–12.3; p<.001) for the low ETVSS group. A patient with moderate ETVSS reveals a 2.2-fold chance of ETV failure than a patient with high ETVSS (95 % CI 1.1–4.6; p=.03).

Secondary ETV
Mean ETVSS for the group with secondary ETV (n=20) was 70 (SD, 9.7), and actual overall ETV success rate after 6 months was 75.0 %. After 36 months (n=16), mean ETVSS was 68.8 (SD, 10.3), and the success rate dropped to 43.8 %.

Repeated ETV
Eventually, 20 patients required repeated ETV; 18 of 20 patients with minimal follow-up of 6 months were eligible for short-term analysis. The interval between

Table 3: Stratified success in 6 months’ period

<table>
<thead>
<tr>
<th>Mean ETVSS (SD)</th>
<th>Successful ETV (n = 73)</th>
<th>Failed ETV (n = 31)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ETVSS (≤ 40)</td>
<td>37.1 (6.86)</td>
<td>4/17 (23.5 %)</td>
</tr>
<tr>
<td>Moderate ETVSS (50–70)</td>
<td>63.2 (8.87)</td>
<td>34/47 (72.3 %)</td>
</tr>
<tr>
<td>High ETVSS (≥ 80)</td>
<td>82.0 (4.05)</td>
<td>35/40 (87.5 %)</td>
</tr>
</tbody>
</table>

Table 4: Stratified success in 36 months’ period

<table>
<thead>
<tr>
<th>Mean ETVSS (SD)</th>
<th>Successful ETV (n = 41)</th>
<th>Failed ETV (n = 43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low ETVSS (≤ 40)</td>
<td>37.7 (5.99)</td>
<td>2/13 (15.4 %)</td>
</tr>
<tr>
<td>Moderate ETVSS (50–70)</td>
<td>62.1 (9.05)</td>
<td>17/38 (44.7 %)</td>
</tr>
<tr>
<td>High ETVSS (≥ 80)</td>
<td>81.5 (3.64)</td>
<td>22/33 (66.7 %)</td>
</tr>
</tbody>
</table>
the first and second surgery was for each patient at least 3 months with a median time between first and repeated ETV of 15.8 months (IQR, 9.2–32.0). In 14 of 18 (77.8 %) patients, the re-ETV was successful for the 6-month follow-up period. The mean ETVSS for these patients was 68.9 (SD, 11.8). Sixteen patients with minimal follow-up of 36 months were eligible for long-term analysis; the mean ETVSS was 67.5 (SD, 11.8). In 10 of 16 (62.5 %) patients, the re-ETV treatment was successful in the long-term.
Late ETV failure
Late ETV failure is defined as failure of ETV between 6 and 36 months. Sixteen of 43 (37.2 %) had late ETV failure after a median period of 15.8 months (IQR, 9.6–26.8). Comparing patients with “late ETV failures” (n=16) vs. “early ETV failures” within 6 months (n=31) revealed a significantly higher mean ETVSS in the first group [late vs. early ETV failure, 68.8 (SD, 12.6) vs. 51.6 (SD, 16.6), respectively; mean difference of 17.1 (95 % CI 7.6–26.7); p=.001]. Median age in months at first ETV, 79.1 (IQR, 9.7–132.5) and 2.4 (IQR, 0.4–19.1), p=.002, differed significantly between patients with late ETV failure and patients with early ETV failure, respectively.

Mortality
As previously stated, ten patients died before the 6-month follow-up criterion was met. During follow-up, mortality rate was 11.5 %. Twelve of 104 children died, with a mean age 6.7 years (SD, 4.3; min, 1.7; max, 15.2). The underlying etiology for hydrocephalus involved: aqueductal stenosis (n=2), non-tectal brain tumor (n=7), and other (n=3). Six patients received subsequent hydrocephalus treatment prior to death. One patient died of shunt dysfunction. The remaining 11 patients died independent of hydrocephalus treatment, i.e., by: malignancy (n=7), epilepsy (n=1), hemolytic–uremic syndrome after meningitis (n=1), acute respiratory distress syndrome after sepsis (n=1), and unknown cause (n=1).

Discussion
In the present study, we provide data regarding the short-term and long-term predictive adequacy of the ETVSS. We found significantly higher mean predicted probability of ETV success in children with successful than failed ETVs for both follow-up periods. Furthermore, the model discrimination, quantified by the area under the ROC curve, was found to be adequate. Therefore, short-term and long-term analyses reveal that ETVSS is a suitable predictive model. Kulkarni et al. developed the ETVSS model. In their internal validation set, the C-statistic (equivalent of the area under the ROC curve) was 0.68. Naftel et al. provided the first external validation of the ETVSS for the 6-month period,
with a C-statistic of 0.74 (95% CI 0.65–0.83). For the 6- and 36-month periods, we found a C-statistic of 0.82 (95% CI 0.71–0.92) and 0.73 (95% CI 0.62–0.84), respectively.

Durnford et al. performed a retrospective analysis for both 6- and 36-month follow-up periods. They found an inverse relationship between short- and long-term follow-up. At the 6-month follow-up period, there was no significant difference between the mean ETVSS for patients with successful vs. patients with failed ETV. In comparison, for the 36-month follow-up period, the mean ETVSS differed significantly in favor of the patients with successful ETV. These findings suggest a positive selection of ETV patients in the long-term group. In contrast to these findings, we report a decreased long-term predictive adequacy. In our study, late failures occurred both in patients with high (14%) and moderate (21%) ETVSS (Kaplan–Meier survival curve, Fig. 2), whereas Durnford et al. reported that late ETV failures are predominantly confined to the moderate ETVSS category.

In accordance with literature, we observed that a large proportion of patients, 62.8%, revealed an early ETV failure. However, we also observed a relatively large proportion of ETV failures after the first 6-month period (about 40 vs. 20% by Durnford et al.). This relatively large group of patients with late failure in spite of high or moderate ETVSS in our series might be explained by selection bias in a historical series. It may also be postulated that other factors than the elements of the ETVSS may be involved in order to explain late failure after ETV.

Comparison of patient characteristics between the groups with early and late ETV failure revealed a significantly younger age and lower ETVSS in the first group. In literature, late ETV failure is described with potentially fatal consequences. Kadrian et al. reported that age is the only significant factor to predict long-term ETV success.

In 78%, re-ETV appeared successful after an evaluation period of 6 months. This relatively high re-ETV success rate has also been reported in literature and may implicate that re-ETV could be considered before proceeding to CSF diversion by means of a VP shunt. Especially, analysis of the moderate ETVSS category could elucidate whether a patient should be treated by means of ETV or VP shunt. This decision will
be based on the personal judgment and preference of the treating surgeon in consultation with patient and parents. More in-depth analysis of the moderate ETVSS group was performed in order to determine which variables may explain the difference in performance of the ETVSS model. The main characteristic differing between failure and success of ETV treatment in this category is patient age at ETV (Table 6). The median age at first ETV is significantly higher in successful ETV for both the short- and long-term follow-up periods. This could suggest that the influence by age at which the ETV is performed might be of pivotal importance. The success rate for the moderate ETVSS group might be improved by attributing more weight to the age factor.

We recognize some limitations to our study. The present study concerns a retrospective design with a limited sample size. However, a randomized controlled prospective design would probably not apply to ethical standards, since individual choices between ETV and VPD treatment options should still depend upon the best predicted benefit (ETV success scores) in the first place. We cannot exclude that multiple considerations before ETV treatment have caused a selection bias. Some hydrocephalus patients have a problematic treatment course with multiple shunt revisions and difficulty finding correct shunting profile. In such patients in whom ETV placement could be regarded
as a last resort, the major advantage of shunt independence could outweigh the limited chance of success. In this specific “salvage” category, risk assessment should therefore be interpreted differently.\textsuperscript{20} For neurosurgeons considering treating hydrocephalus in a pediatric patient by means of ETV, the ETVSS provides a useful tool in everyday practice. The total score is easy to implement, and the calculated chances of success during the first 6 months are sufficiently validated in previously mentioned series. With the application of the score, the treatment of hydrocephalus could become more uniform and transparent. In addition to predicting chances of successful ETV treatment for individual patients, the ETVSS (when consistently used by future authors) may contribute to a more reliable comparison of pediatric cohorts of hydrocephalic children treated with ETV described in literature.
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References


