Endoscopic Third Ventriculostomy Vs Cerebrospinal Fluid Shunt in the Treatment of Hydrocephalus in Children: A Propensity Score–Adjusted Analysis

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BACKGROUND: Endoscopic third ventriculostomy (ETV) has preferentially been offered to patients with more favorable prognostic features compared with shunt.

OBJECTIVE: To use advanced statistical methods to adjust for treatment selection bias to determine whether ETV survival is superior to shunt survival once the bias of patient-related prognostic factors is removed.

METHODS: An international cohort of children (≤ 19 years of age) with newly diagnosed hydrocephalus treated with ETV (n = 489) or shunt (n = 720) was analyzed. We used propensity score adjustment techniques to account for 2 important patient prognostic factors: age and cause of hydrocephalus. Cox regression survival analysis was performed to compare time-to-treatment failure in an unadjusted model and 3 propensity score—adjusted models, each of which would adjust for the imbalance in prognostic factors.

RESULTS: In the unadjusted Cox model, the ETV failure rate was lower than the shunt failure rate from the immediate postoperative phase and became even more favorable with longer duration from surgery. Once patient prognostic factors were corrected for in the 3 adjusted models, however, the early failure rate for ETV was higher than that for shunt. It was only after about 3 months after surgery did the ETV failure rate become lower than the shunt failure rate.

CONCLUSIONS: The relative risk of ETV failure is initially higher than that for shunt, but after about 3 months, the relative risk becomes progressively lower for ETV. Therefore, after the early high-risk period of ETV failure, a patient could experience a long-term treatment survival advantage compared with shunt. It might take several years, however, to realize this benefit.

KEY WORDS: Endoscopy, Hydrocephalus, Pediatrics, Propensity score

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The growing enthusiasm for endoscopic third ventriculostomy (ETV) is fueled largely by the assumption that ETV is inherently superior to shunt in the treatment of hydrocephalus. This assumption, however, has never been directly proven. No randomized studies comparing ETV with shunt exist (although one is currently underway[1]). Enthusiasm for ETV has instead been engendered by several cohort studies that have suggested a lower failure incidence for ETV than has traditionally been seen with shunt.[2-6] Very few studies have tried to directly compare ETV and shunt cohorts in a single analysis.[7,8] These studies, however, have not been able to adequately account for the effect of treatment selection bias. That is, patients selected for ETV are usually older and have aqueduct stenosis as the cause of their hydrocephalus. These appear to be favorable prognostic factors for treatment, so nonrandomized comparisons of ETV and shunt are clouded by treatment selection bias that could give ETV the illusion of superiority. In the absence of randomized data, this bias can be addressed, at least partially, only with advanced statistical modeling techniques. Therefore, our objective

ABBREVIATIONS: ETV, endoscopic third ventriculostomy

was to compare the treatment failure of ETV and shunt in a large cohort of children using the statistical method of propensity scores to account for treatment selection bias. Propensity scores are a well-established means of accounting for baseline differences in patient groups to isolate the effect of a surgical treatment itself.[9,10] Our analysis helps answer the question, Is ETV survival truly superior to shunt survival once the bias of patient-related prognostic factors is removed?

PATIENTS AND METHODS

Population

All patients were ≤ 19 years of age; had newly diagnosed, previously untreated high-pressure hydrocephalus; and were treated by pediatric neurosurgeons at specialized centers. The ETV cohort was collected from a recent international initiative (patient recruitment, 1989-2006 from Canada, Israel, and the United Kingdom).[11] The shunt cohort was collected from 2 prospective trials (with permission granted from the principal investigators of each trial for analysis of data), the Shunt Design Trial[12] (patient recruitment, 1993-1995 from Canada, France, the Netherlands, and the United States) and the Endoscopic Shunt Insertion Trial[13] (patient recruitment, 1996-1999 from Canada, the Netherlands, the United Kingdom, and the United States). These 2 trials involved multiple international centers and compared technical variations in cerebrospinal fluid (CSF) shunting. Both studies demonstrated no difference in outcome in the treatment arms; therefore, all patients were analyzed collectively for this study. All data were anonymized, and data collection adhered to local research ethics protocols.

Failure of treatment was defined as any subsequent surgical procedure for definitive CSF diversion or death related to hydrocephalus management.

Statistical Analysis

To account for treatment selection bias and potential confounding, we calculated propensity scores, which represent the probability of receiving ETV rather than shunt, conditional on observed covariates. We used age at the time of treatment and cause of hydrocephalus as the covariates in a logistic regression model; treatment with ETV was the dependent variable. We limited the model to age and origin because the literature supports these as the most important confounders (ie, variables related to both treatment allocation and treatment failure).[14-18] We recognize that other factors are involved in the surgical decision to proceed with ETV rather than shunt, but for propensity score modeling, it is important to include those factors that might be prognostic of outcome. Age was categorized as < 1 month, 1 to < 6 months, 6 to < 12 months, 1 to < 10 years, and ≥ 10 years.[11] Cause of hydrocephalus was categorized as aqueduct stenosis, myelomeningocele, postintraventricular hemorrhage, brain tumor, and other.

We performed survival analysis using Cox proportional-hazards models to provide a hazard ratio for ETV failure relative to shunt failure. The hazard ratio is essentially the instantaneous risk of ETV failure compared with shunt failure at a given moment in time (values > 1 indicate a higher chance of ETV failure than shunt failure). We discovered, however, a violation of the proportional-hazards assumption based on visual inspection of the treatment survival curves (using Kaplan-Meier method) and significance of the interaction of time and treatment ($P < .001$). This meant that the risk of ETV failure compared with shunt failure was not constant after surgery but rather changed as a function of time after surgery. Therefore, we explored 3 alternative models that would allow the hazard ratio to change over time: piecewise (allowing the hazard ratio to change as a step function of time) and 2 time-by-treatment interactions (one with time as a linear function and the other as a logarithmic function). On the basis of likelihood ratio tests, the data seemed to be best modeled with a log10(time)-by-treatment interaction. Thus, this time-dependent interaction term was included in all Cox regression models. We first performed an unadjusted Cox model in which only treatment and the time-treatment interaction were included. To account for the potential confounders, we used 3 different propensity score methods, each of which would balance or adjust for the imbalance in patient prognostic factors:

1. Propensity score–adjusted Cox model in which propensity score (on the probability scale) was added as a covariate, along with treatment and time-treatment interaction.
2. Cox model stratified by quintile of propensity score[19,20] in which we divided the sample into 5 approximately equally populated strata based on propensity score. We tested for balance in the confounders within each quintile with a 2-sample Kolmogorov-Smirnov test to see whether the distribution of the propensity scores (and hence the confounders) was comparable between the ETV and shunt patients.[21] We then performed a Cox model with stratification on the quintiles.
3. Matched-sample Cox model for which we created a matched sample based on propensity score to balance confounders between treatment groups. We used an exact matching algorithm without replacement to match an ETV patient to a shunt patient whose propensity score was an exact match. This ensured that there was balance in confounders (age and origin). We performed a Cox model within the matched sample containing treatment and time-treatment interaction as the variables. To account for the matching, the analysis was stratified by matched pairs.[22]

All analyses were done with SPSS Advanced Statistics 17.0 (SPSS Inc, Chicago, Illinois).

RESULTS

The characteristics of the 1209 patients are listed in Table 1. As expected, there was imbalance in age and origin (both $P < .001$, χ^2 test) between the treatment groups, with a preponderance of poor prognostic factors in the shunt group (more young patients and those with myelomeningocele and intraventricular hemorrhage).

Propensity Scores

We calculated propensity scores from a logistic regression model using age and origin of hydrocephalus as the covariates. The predicted probability of receiving ETV treatment (propensity score) was calculated for each patient (ie, a higher score means a greater probability of receiving ETV based on the patient's age and origin of hydrocephalus). The distribution of propensity scores by treatment is shown in Figure 1, and mean values are given in Table 1. Within 3 of the 5 quintiles of propensity score, the 2-sample Kolmogorov-Smirnov test was not significant (all $P > .08$), indicating a reasonable balance in the confounder distribution between ETV and shunt patients within these quintiles. There was some imbalance, however, in the highest and third-highest quintiles ($P < .05$). The matching algorithm was successful in finding 216 ETV-shunt pairs with identical propensity scores. This sample was perfectly balanced in all age and origin categories (ie, no mismatches at all); the matched sample characteristics are shown in Table 2.

TABLE 1. Patients Characteristics[a]

Variable	ETV	Shunt	Overall
Patients, n	489	720	1209
Years during which patients were treated	1989-2006	1993-1999	
Countries in which patients were treated	Canada, Israel, UK	Canada, France, Netherlands, UK, US	
Age at treatment, n (%)			
< 1 mo	36 (7.4)	234 (32.5)	270 (22.3)
1 to < 6 mo	78 (16.0)	240 (33.3)	318 (26.3)
6 to < 12 mo	35 (7.2)	83 (11.5)	118 (9.8)
1 to < 10 y	206 (42.1)	122 (16.9)	328 (27.1)
≥ 10 y	134 (27.4)	41 (5.7)	175 (14.5)
Cause of hydrocephalus, n (%)			
Stenosis of cerebral aqueduct	168 (34.4)	53 (7.4)	221 (18.3)
Brain tumor	175 (35.8)	48 (6.7)	223 (18.4)
Postintraventricular hemorrhage	53 (10.8)	161 (22.4)	214 (17.7)
Myelomeningocele	10 (2.0)	178 (24.7)	188 (15.6)
Other	83 (17.0)	280 (38.9)	363 (30.0)
Propensity score, mean (SD)	0.65 (0.26)	0.23 (0.23)	0.40 (0.32)

[a] ETV, endoscopic third ventriculostomy; SD, standard deviation.

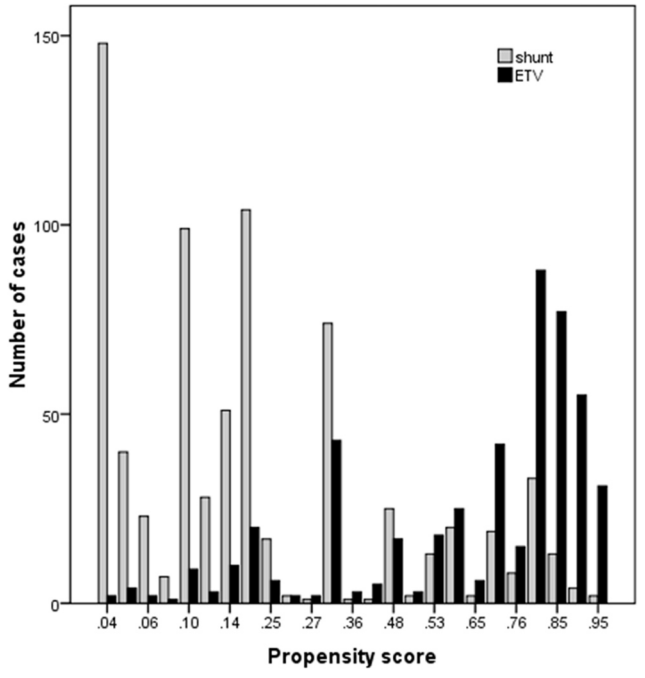

FIGURE 1. *Bar chart showing the distribution of propensity scores for endoscopic third ventriculostomy (ETV) and shunt patients.*

TABLE 2. Matched Sample Patients' Characteristics[a]

Variable	ETV	Shunt	Overall
Patients, n	216	216	432
Age at ETV, n (%)			
< 1 mo	26 (12.0)	26 (12.0)	52 (12.0)
1 to < 6 mo	49 (22.7)	49 (22.7)	98 (22.7)
6 to < 12 mo	25 (11.6)	25 (11.6)	50 (11.6)
1 to < 10 y	86 (40.0)	86 (40.0)	172 (40.0)
≥ 10 y	30 (13.9)	30 (13.9)	60 (13.9)
Cause of hydrocephalus, n (%)			
Stenosis of cerebral aqueduct	46 (21.3)	46 (21.3)	92 (21.3)
Brain tumor	41 (19.0)	41 (19.0)	82 (19.0)
Postintraventricular hemorrhage	40 (18.5)	40 (18.5)	80 (18.5)
Myelomeningocele	6 (2.8)	6 (2.8)	12 (2.8)
Other	83 (38.4)	83 (38.4)	166 (38.4)
Propensity score, mean (SD)	0.49 (0.25)	0.49 (0.25)	0.49 (0.25)

[a] ETV, endoscopic third ventriculostomy; SD, standard deviation.

Cox Models

The time-treatment interaction was significant in all Cox models, and because of this time-dependent nature, the hazard ratios are displayed as a function of time in Figure 2. This figure shows how the risk of ETV failure relative to shunt (the hazard ratio) changes over time. In all models, the hazard ratio decreases with

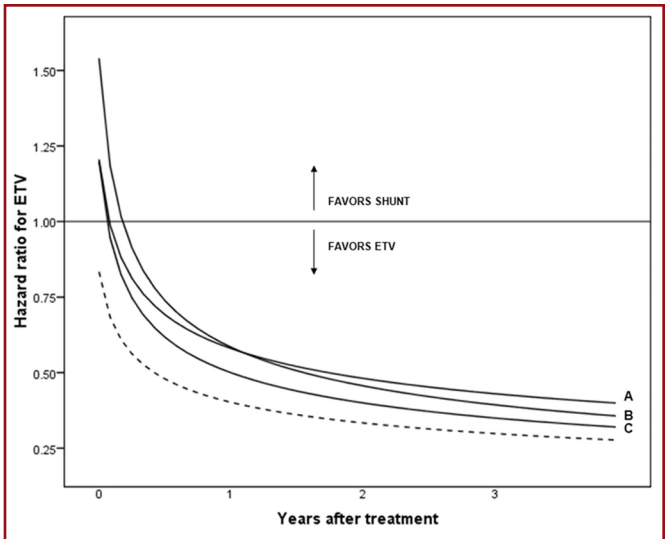

FIGURE 2. *Graph showing the treatment failure hazard ratios for endoscopic third ventriculostomy (ETV) relative to shunt as a function of time for the unadjusted Cox model (dotted line) and each of the 3 adjusted Cox models: propensity score as covariate (solid line A), propensity score matched (solid line B), and propensity score stratified (solid line C). See text for explanation.*

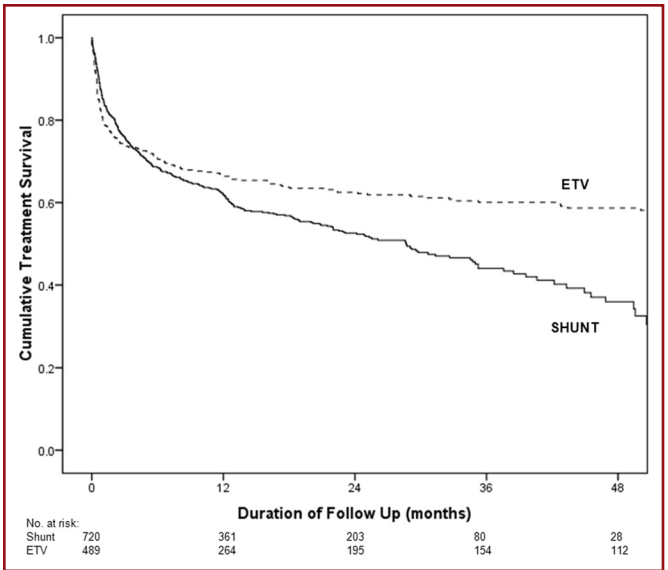

FIGURE 3. *Survival curve showing cumulative treatment survival for patients treated with endoscopic third ventriculostomy (ETV; dotted line) and shunt (solid line). These curves are not adjusted for differences in patient prognostic factors.*

time, meaning that the risk of ETV failure becomes progressively lower relative to shunt with increasing time from surgery. In the unadjusted model, however, the hazard ratio favors ETV from the outset and then becomes even more favorable with time (dotted line in Figure 2). For all 3 confounder-adjusted models, however, the hazard ratios initially strongly favor shunt but, over time, progressively favor ETV. It is not until about 3 months after surgery that the risk of ETV failure actually becomes lower than the risk of shunt failure (ie, the point at which the hazard ratio dips below 1).

The effect of adjusting for patient prognostic factors can also be seen by comparing the survival curves in Figures 3 and 4. Figure 3 compares ETV and shunt survival in the total sample of 1209 patients and without any adjustment for the differences in patient prognostic factors between the 2 groups. It shows a dramatic benefit in ETV survival at 4 years compared with shunt. Figure 4 compares ETV and shunt survival within the matched sample in which patient prognostic factors are equalized between the 2 groups. In contrast to Figure 3, Figure 4 shows an advantage in shunt survival until about 3 years, at which point ETV begins to show a marginal benefit.

DISCUSSION

The assumption of ETV superiority to shunt has never been proven. In the absence of randomized data, our study represents the best analysis currently available to compare the failure rates of these 2 competing treatments for childhood hydrocephalus. In this study, we have discovered 2 important new findings that are relevant to clinical decision making about ETV. First, we have shown that ETV has a higher rate of early postoperative failure relative to shunt. This early risk of failure is at least 20% higher than shunt; ie, the early hazard ratio is > 1.2 (see Figure 2). This likely reflects the selection of patients for whom ETV was physiologically unsuitable. Second, we have shown that, after about 3 months, the relative risk of failure of ETV is lower than that of shunt (ie, the point at which the hazard ratio in Figure 2 crosses below 1) and then becomes progressively lower with more time. At 2 years, for example, the risk of ETV failure is roughly half the risk of shunt failure; ie, the hazard ratio is approximately 0.5 (see Figure 2). Although this second point might have been suspected by ETV proponents, no previous study has been able to show this in a statistically valid comparison with a large shunt cohort. This does not necessarily mean that the cumulative survival of ETV treatment is superior to shunt after 3 months. In fact, it is not. Rather, it means that for patients who have not yet experienced a treatment failure after 3 months, the instantaneous risk of experiencing a first failure any time thereafter appears slightly lower for ETV patients than shunt patients.

The combination of our 2 findings has direct clinical implications. On the one hand, it stresses the value of appropriate patient selection for ETV to maximize the chance of early ETV success. Our recently developed and validated ETV Success Score, for example, could be used to minimize these early failures and select only those patients who would benefit most from ETV.[11] If restricted to those expected to have a low early failure rate, then our data suggest that ETV would be truly superior to shunt. The other implication, however, is that because the long-term risk of ETV failure does appear to be lower than that for shunt, there could be some rationale to attempting ETV in less-than-ideal candidates because a successful ETV might confer long-term benefits

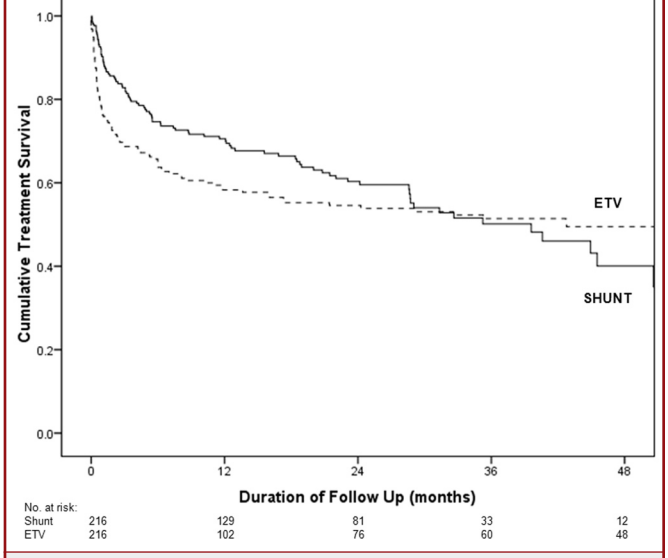

FIGURE 4. *Survival curve showing cumulative treatment survival for patients in the propensity score—matched sample treated with endoscopic third ventriculostomy (ETV; dotted line) and shunt (solid line). For these curves, patient prognostic factors have been balanced (adjusted for).*

over shunt. For children whose lifetime hydrocephalus treatment will span several decades, this advantage could be beneficial. However, in many cases, it will take several years for patients to truly benefit from the small yearly survival advantage of ETV, and only if they survive the high-risk early period. In patients whose risk of early ETV failure is very high, however, no benefit is likely to be gained compared with CSF shunt.

The strength of our analysis lies in the large sample size and the advanced statistical techniques we used to adjust for treatment selection bias. Although our use of propensity scores and time-dependent modeling might appear overly complex, it was essential to provide a meaningful comparison of the 2 treatments. Unadjusted analysis provided a falsely optimistic assessment of ETV survival compared with shunt. This is demonstrated by comparing the unadjusted survival curve (Figure 3) with the propensity score—matched survival curve (Figure 4). Recognizing that there is no universally accepted "gold standard" technique for confounder adjustment, we used 3 different techniques, each of which has some limitations. In the matched sample survival curve presented in Figure 4, it is difficult to make direct clinical inference because it is essentially comparing a heterogeneous "moderate-risk" cohort in which the best-prognosis ETV patients and the worst-prognosis shunt patients have been removed. In addition, in using stratification on propensity score quintiles, we found some residual imbalance in some of the quintiles, which could slightly limit the effectiveness of this technique. Nevertheless, the results of all 3 confounder adjustment techniques were virtually identical to each other, as evidenced by the near overlap of the 3 solid hazard ratio curves in Figure 2. This finding gives us added confidence in the validity of our results.

We recognize that our study has limitations. Our statistical adjustments accounted for only 2 confounders, age and origin of hydrocephalus. Although the literature does not support the presence of any other important prognostic factors, it is possible that some hidden confounders remain for which our model did not account. The magnitude of the bias associated with such confounders, however, would likely be quite small. We also recognize that there are other factors that go into the surgical decision of shunt versus ETV (including evidence of discreet CSF obstruction, personal comfort/aggressiveness with neuroendoscopy, etc). Although our modeling did not account for these factors, this does not affect the validity of our analysis. The use of age and origin as the only predictors was still highly predictive of the final treatment allocation, even without the inclusion of the many other factors involved in these decisions (as can be seen by the very divergent distributions of the calculated propensity scores for ETV versus shunt in Figure 1). That is all that is required for a propensity score model to be effective, as ours was. Although our large cohort was accrued from different international centers over a long period of time, we have previously shown that these factors did not affect ETV performance,[11] nor have they been shown to affect shunt survival. Additionally, the diversity in our sample only enhances its external validity. Treatment failure for the ETV cohort was determined by a surgeon without external review, whereas for the shunt cohort, the failed cases were independently adjudicated.[12,13] Therefore, the standard for declaring failures might be different. If anything, however, this difference should have favored ETV. Our follow-up data included meaningful survival data only to 4 years after treatment. Longer follow-up data are still important to assess the delayed trends in failure associated with both treatments. Previously published works, however, including from our group,[11] have shown the long-term durability of ETV and, on the other hand, the continued attrition of shunts over time.[23] Probably the most important limitation of our analysis, however, was that it examined only the need for a single repeat surgery. We did not measure other outcomes such as the morbidity of treatment and complications (eg, shunt infection, forniceal injury), need for multiple surgeries, duration of hospitalizations, and impact on quality of life, which are admittedly important and need further study.

CONCLUSION

We have, for the first time, performed a comparative analysis of ETV and shunt using advanced statistical methods to adjust for important confounders. This study demonstrated that the relative risk of ETV failure is initially higher than that for shunt, but after about 3 months following surgery, the relative risk becomes progressively lower for ETV. Therefore, if patients survive the early high-risk period of ETV failure, they could experience long-term treatment survival advantage compared with shunt. It might take several years, however, for this survival advantage to be realized. Although ours is the most rigorous comparison of these 2 treatments currently in the literature, it is not a replacement for a randomized trial and should be interpreted in light of its inherent limitations.

Appendix

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Disclosure

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