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ORIGINAL PAPER

Surgery for hydrocephalus in sub-Saharan Africa versus developed nations: a risk-adjusted comparison of outcome

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Abstract

Purpose Surgery for children in developing nations is challenging. Endoscopic third ventriculostomy (ETV) is an important surgical treatment for childhood hydrocephalus and has been performed in developing nations, but with lower success rates than in developed nations. It is not known if the lower success rate is due to inherent differences in prognostic factors.

Methods We analyzed a large cohort of children (≤20 years old) treated with ETV in developed nations (618 patients from Canada, Israel, United Kingdom) and developing nations of sub-Saharan Africa (979 patients treated in Uganda). Risk-adjusted survival analysis was performed.

Results The risk of an intra-operative ETV failure (an aborted procedure) was significantly higher in Uganda regardless of risk adjustment (hazard ratio (HR), 95% confidence interval (CI), 11.00 (6.01 to 19.84) $P<0.001$). After adjustment for patient prognostic factors and technical variation in the procedure (the use of choroid plexus cauterization), there was no difference in the risk of failure for completed ETVs (HR, 95% CI, 1.04 (0.83 to 1.29), $P=0.74$).

Conclusions Three factors account for all significant differences in ETV failure between Uganda and developed nations: patient prognostic factors, technical variation in the procedure, and intra-operatively aborted cases. Once adjusted for these, the response to completed ETVs of children in Uganda is no different than that of children in developed nations.

Keywords Developing countries · Endoscopy · Hydrocephalus · Pediatrics · Risk adjustment

Canadian Pediatric Neurosurgery Study Group (see Appendix 1 for list of members)

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Introduction

The surgical treatment of children in developing nations can be challenging. Hydrocephalus is a cause of major morbidity for children across the globe and can now often be treated with an endoscopic third ventriculostomy (ETV). Since the early 1990s, the success of ETV in developed nations has become well established [9]. In developing countries, ETV has a possibly even more beneficial role in hydrocephalus management because many of the long-term complications associated with shunting can have worse consequences in settings with limited access to immediate neurosurgical care [15]. But can ETV be performed in developing nations with outcomes similar to those achieved in developed nations? Others have shown this to be difficult for pediatric heart surgery, for example [10]. The recent large experience from Uganda in sub-Saharan Africa has proven that ETV can be performed successfully in developing nations [16–18], but the overall success rate of the procedure appears to be lower than in developed nations [9, 19]. The reasons for this lower success rate have not been studied. There are inherent differences between the situation in Uganda and developed nations: Ugandan patients are younger at presentation, have a preponderance of post-infectious hydrocephalus, and have no access to pre-operative magnetic resonance imaging (MRI). Some of these are known risk factors for ETV failure [9]. If we could account for the obvious differences in risk factors for ETV failure, would the response of children to ETV in Uganda still be worse than in developed nations? This question has not been answered.

Our collaborative group was in the unique position of being able to bring together a large sample of data from ETV treatment in Uganda, Canada, United Kingdom, and Israel [9, 19]. Our objective was to describe and explain how the failure rate of ETV differed between children from sub-Saharan Africa and those from developed nations. We hypothesized that, once the obvious high-risk patient factors were accounted for, there would be no difference between the outcomes of these two populations of children. If that were the case, then it would confirm that some high-level pediatric surgery can be performed in settings across the world with similar outcomes. As well, it might allow us to more confidently extrapolate research findings from one setting to the other and would support the concept of collaborative global research. We adopted the methodology of a risk-adjusted multivariable analysis, a well-described technique for the comparison of surgical performance between centers or countries [1, 2].

Methods

Population The data for this analysis came from two previously described sources [9, 19]. The developed nations' ETV cases were the result of an international collaboration that involved 12 pediatric neurosurgery centers in Canada, Israel, and United Kingdom [9]. We collected data from all ETV procedures on patients 19 years or under and performed consecutively at these centers. The period of data collection varied by center, ranging as far back as 1989 to as recent as 2006, although 95.4% of cases were performed since 1995. Data from five centers (358 patients) were collected entirely prospectively; the remaining centers (260 patients) collected data retrospectively. The Uganda ETV cases were consecutive patients 20 years of age and under who were treated at CURE Children's Hospital of Uganda in Mbale between 2001 and 2007 [19]. This hospital was opened in 2001 with the mission of providing high-quality treatment of neurosurgical diseases, including hydrocephalus, for children in Uganda and neighboring nations. The procedures were performed by an American neurosurgeon and locally trained neurosurgeons. Data were collected prospectively. The majority of children were from Uganda, but others were from Kenya, Tanzania, Malawi, Somalia, Rwanda, Congo, and Mauritius.

All patients had symptomatic, high-pressure hydrocephalus. Some had previous treatment with a cerebrospinal fluid (CSF) shunt and presented with a shunt malfunction for which ETV was performed. Only patients who had at least 6 months of follow-up were included. In cases of multiple ETV procedures on the same patient, only data from the first procedure were included. Data from some of these patients have appeared in previous publications [3–6, 8, 9, 11–14, 16–19]. All data were anonymized and data collection adhered to local research ethics protocols.

The procedure performed on all patients was a standard ETV through a frontal burr hole trajectory, with a fenestration made either in the floor of the third ventricle and/or lamina terminalis using a rigid or flexible endoscope.

Failure of ETV was defined as any subsequent surgical procedure for definitive CSF diversion or death related to hydrocephalus management. Any ETV procedure that had to be aborted for technical reasons was also considered an early failure (even though many of these did have a successful ETV at a later date).

Differences in the management protocol The differences in the management protocol between Uganda and developed nations included the following:

1. Imaging: Ugandan patients received pre-operative imaging with ultrasound and/or computed tomography. MRI, a standard pre-operative imaging modality in developed countries, was not available.
2. Selection of patients for ETV: In developed nations, the decision to perform ETV was based on surgeon's discretion after a discussion with the family. The philosophy at these centers was to reserve ETV for reasonably favorable candidates, although some seemingly poor candidates for ETV were treated. In Uganda, ETV was the primary treatment offered to all children presenting with hydrocephalus, regardless of age or etiology, after a discussion with the family about the treatment alternatives. Shunts were used only if ETV failed, could not be performed for technical reasons, or was preferred by the family.
3. Technical variations in the ETV procedure: Starting in January 2003, choroid plexus cauterization (CPC) was

performed in Uganda, whenever technically feasible [16, 18]. This is thought to reduce CSF production and it was hypothesized that this would increase the chance of ETV success. CPC was not used for any patient in the developed nations.

4. Determination of ETV failure: In Uganda, the determination of ETV failure was made on pre-established clinical grounds and supplemented by post-operative imaging (cranial ultrasound or CT) to confirm an increase in ventricle size. Clinical indicators of failure included: continued excessive growth in head circumference and other symptoms or signs of raised intracranial pressure, e.g., bulging fontanelle, sunsetting of the eyes, headaches, and vomiting. Similarly, in developed nations, ETV failure was determined based on clinical grounds and supplemented by imaging assessment which, in this case, often included MRI. In all cases, ETV failure was determined by the individual treating surgeon.

Statistical analyses

We analyzed time-to-ETV failure using Cox proportional hazards regression modeling. In order to perform a risk-adjusted analysis to account for inherent differences between these populations, the following variables were adjusted for:

1. Age and etiology: We recognized that, aside from the management differences described above, the Ugandan patients would have a higher proportion of poor candidates for ETV, based on their very young age and etiology (mostly post-infectious and myelomeningocele). Therefore, we needed to risk-adjust the model for these two variables. We had previously developed a numerical means of adjusting for the risk of age and etiology on ETV success: the ETV Success Score (ETVSS) [9]. This is a linear scoring system that quantifies the chances of ETV success based on the patient's age, etiology of hydrocephalus, and presence of a previous shunt. The metric of the ETVSS ranges from 0 (essentially no chance of ETV success at 6 months) to 90 (approximately 90% chance of ETV success at 6 months). In effect, the ETVSS is a single score that adjusts for differences in prognostic features: a low ETVSS means that the patient is expected to be at high risk of failure and a high ETVSS means that the patient is expected to be at low risk of failure. Therefore, this allows one to compare the observed failure rate between patient populations while adjusting for differences in these patient prognostic factors. This would then provide the *additional risk of failure* that is not accounted for by age and etiology differences alone. The use of prediction scores for risk-adjusted analysis for surgical audit purposes is well described [1, 20]. The ETVSS was calculated for every patient in the sample and used as an independent variable in the regression models.
2. Choroid plexus cauterization: The use of CPC in some cases in Uganda was the only relevant technical difference between the two populations. Therefore, CPC (defined as complete bilateral CPC) was also used as an independent variable.

We tested regression models with the following variables: (a) an unadjusted model with only treatment location (Uganda vs. developed nations), (b) a risk-adjusted model adjusted for ETVSS alone, and (c) a risk-adjusted model adjusted for ETVSS and whether CPC was performed (yes vs. no). The proportional hazards assumption for each independent variable was confirmed by testing for interaction with time (all P-values >0.7). Examination of survival curves, however, revealed that the very early failure rate for the Uganda patients was much higher than in the developed nations, due to a much higher incidence of aborted cases (usually due to unfavorable anatomy or poor visibility from murky CSF). Therefore, piece-wise proportional hazards regression was used to generate hazard ratios (HR), indicating the relative risk of ETV failure between Uganda and developed countries, in two time periods following ETV: within the first post-operative day (to indicate the relative risk of intra-operative failure, i.e., aborted cases) and after the first post-operative day (to indicate the relative risk of failure for completed ETV cases). HRs greater than 1 indicated that ETV failure is higher in Uganda than in developed nations. All variance inflation factors were less than 3, suggesting no concerning collinearity among the variables [7].

All analyses were done with SPSS Advanced Statistics 17.0 (SPSS Inc., Chicago, IL, USA). This study received local ethical approval at all participating centers.

Results

A total of 1,597 patients were included in this analysis and their characteristics are listed in Table 1. As expected, there was a large discrepancy between Uganda and developed countries in age, etiology, and number of intra-operative failures. The median ETVSS was lower in Uganda, indicating that the patient characteristics of the Uganda population put them at a substantially higher predicted risk of ETV failure based on their age and etiology.

Table 1 Patients' characteristics

Variable	Uganda (number (%))	Developed nations (number (%))
Number of patients	979	618
Age		
≤1 month	41 (4.2)	39 (6.3)
1 to <6 months	591 (60.4)	90 (14.6)
6 to <12 months	202 (20.6)	49 (7.9)
1 to <10 years	119 (12.2)	255 (41.3)
≥10 years	26 (2.7)	185 (30.0)
Etiology		
Post-infectious	566 (57.8)	22 (3.6)
Myelomeningocele	117 (12.0)	38 (6.1)
Aqueductal stenosis	0	194 (31.4)
Intra-ventricular hemorrhage	8 (0.8)	80 (12.9)
Tectal tumor	0	182 (29.40)
Non-tectal tumor	0	43 (7.0)
Other	288 (29.4)	59 (9.5)
Previous CSF shunt in place	25 (2.6)	156 (25.2)
Complete choroid plexus cauterization performed	334 (34.1)	0
Median ETVSS	40	80
Number of ETV cases aborted intra-operatively	281 (28.7)	12 (1.9)
Total number of ETV failures	608 (62.1)	263 (42.6)

ETV endoscopic third ventriculostomy, *CSF* cerebrospinal fluid

The unadjusted survival curve, by Kaplan–Meier method, is shown in Fig. 1. As described above, there is a substantial drop-off in the Ugandan survival curve at time "zero", indicating the high proportion of intra-operative failures.

Results of the regression analyses are shown in Table 2. In all models (with or without risk adjustment), the risk of intra-operative ETV failure (aborted cases) was much higher in Uganda than in developed nations (all HR

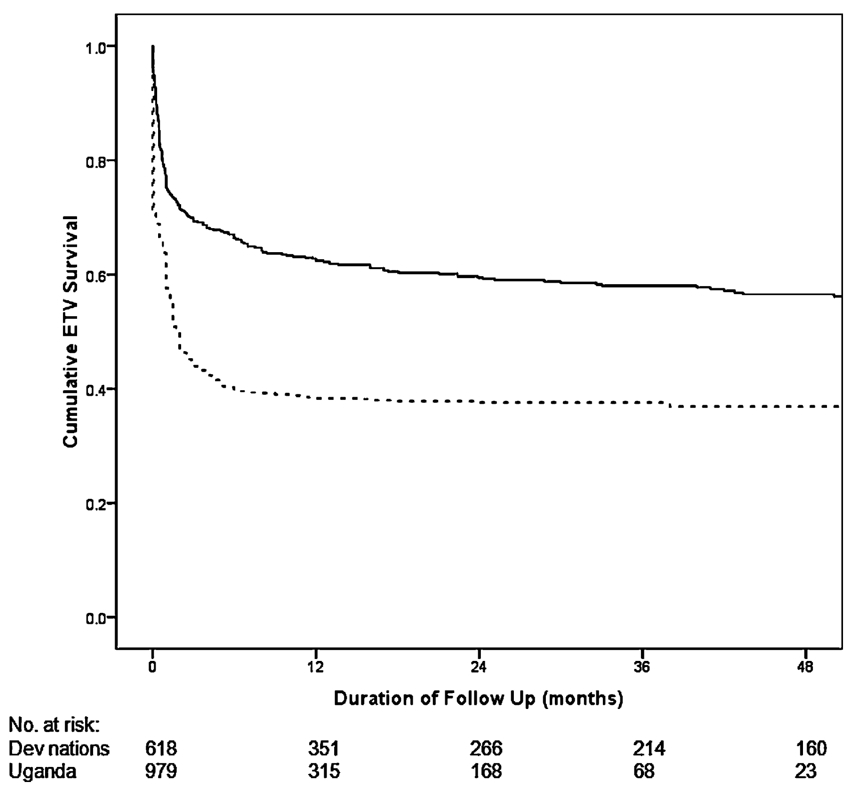

Fig. 1 Survival curve constructed using Kaplan–Meier method, comparing ETV survival in Uganda (*dashed line*) and developed nations (*solid line*)

Table 2 Piece-wise hazard ratio regression models for all cases (n=1,597)

Variable	Hazard ratio for intra-operative ETV failure (aborted case) (95% confidence interval)	Hazard ratio for failure of a successfully completed ETV (95% confidence interval)
Univariable model with no risk adjustment		
Treatment in Uganda (vs. developed nations)	14.78 (8.30 to 26.34) P<0.001	1.20 (1.02 to 1.42), P=0.03
Multivariable model risk-adjusted for ETV Success Score		
Treatment in Uganda (vs. developed nations)	8.26 (4.58 to 14.92), P<0.001	0.68 (0.56 to 0.84), P<0.001
ETV Success Score	0.98 (0.98 to 0.99), P<0.001	0.98 (0.98 to 0.99), P<0.001
Multivariable model risk-adjusted for ETV Success Score and choroid plexus cauterization		
Treatment in Uganda (vs. developed nations)	11.00 (6.01 to 19.84), P<0.001	1.04 (0.83 to 1.29), P=0.74
ETV Success Score	0.99 (0.98 to 0.99), P<0.001	0.99 (0.98 to 0.99), P<0.001
Choroid plexus cauterization performed	0.40 (0.33 to 0.48), P<0.001	0.40 (0.33 to 0.48), P<0.001

greater than 8, all P-values <0.001). The risk of failure of completed ETV cases (i.e., failure after the first post-operative day) varied among the three models. In the unadjusted model, the risk of ETV failure in Uganda was higher (HR=1.20, p=0.03). Once adjusted for ETVSS (which accounted for age and etiology), the risk of ETV failure was actually lower in Uganda than in developed nations (HR=0.68, P<0.001). This appeared to be because of the beneficial effect of CPC (used exclusively in Uganda), because once this was also adjusted for in the final model there was no difference in ETV failure between Uganda and developed nations (HR=1.04, P=0.74). The HRs for completed ETVs are shown graphically in Fig. 2.

Discussion

In a large cohort of children, we performed a risk-adjusted analysis to compare the outcome of ETV between Uganda and developed nations. We found that all significant differences between ETV failures in these settings can be accounted for by three factors: intra-operatively aborted cases, patient prognostic factors as measured by the ETVSS, and the use of CPC. After adjusting for these three factors, the failure rate for ETV in Uganda was virtually identical to that in developed nations. The vast majority of ETV failures in both populations occurred within the first few months of surgery, with very few failures occurring in a delayed fashion. Our results suggest that ETV can be performed in developing and developed nations with similar outcomes.

The strengths of our study include its very large sample size (to our knowledge, the largest collective ETV sample analyzed to date). Most of the data were collected prospectively. We used appropriate and targeted statistical methods to answer our study questions. The limitations of our study include the fact that CPC was not performed in any of the developed nation cases, making its effect more difficult to interpret. The developed nations' sample was accrued over a long period of time and the period of chronological overlap between it and the Ugandan sample was limited to the last 5 years. We have shown before, however, that the

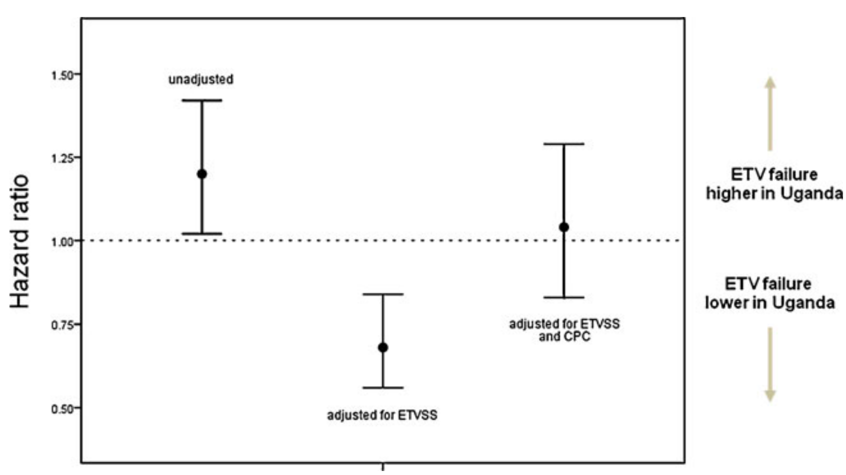

Fig. 2 Forest plot showing the hazard ratio estimates (*solid dot*) and the 95% confidence intervals (*bar lines*) for the unadjusted and adjusted Cox regression models. Hazard ratios greater than 1 indicate a higher risk of ETV failure in Uganda. *ETVSS*, ETV Success Score; *CPC*, choroid plexus cauterization

epoch of treatment had no effect on ETV failure rates in the developed nations' sample [9]. The long-term data available on the Uganda patients were limited due to loss of patient follow-up. This largely limits the strength of our conclusions for long-term ETV outcomes in sub-Saharan Africa but will be the focus of future studies.

It is relevant that the ETVSS prediction score that we used to account for expected prognostic differences in age and etiology was developed purely on patients treated in developed nations [9]. The fact that it also successfully accounted for the prognostic effects of these variables for the Ugandan patients suggests that the relative effect of these features is similar, regardless of location.

Our analysis re-confirms the important beneficial effect of CPC [16, 18, 19]. Risk adjustment for only age and etiology revealed that the failure rate for completed ETVs in Uganda was actually significantly lower than in developed nations. This surprising effect was entirely negated once CPC was introduced into the model.

The high incidence of intra-operatively aborted cases in Uganda was expected. This was attributable to either unfavorable anatomy or murky CSF with poor visibility at the time of ventriculoscopy. This is, perhaps, the most relevant difference between the populations. At least part of this could be explained by the lack of pre-operative MRI in Uganda, which might otherwise have alerted the surgeon to unfavorable anatomy. In developed nations, such patients likely would not have even been offered ETV. In other cases, the lack of visibility was the result of a particularly severe ventriculitis or one which was only partially treated, both of which are rare occurrences in developed nations.

Conclusion

Using a risk-adjusted survival analysis, we have shown that three factors account for all significant differences in ETV failure between Uganda and developed nations: ETV Success Score (which adjusts for age and etiology), choroid plexus cauterization, and intra-operatively aborted cases. Once adjusted for these, the response to completed ETVs among children in Uganda is no different than that among children in developed nations, suggesting that such procedures can be performed across the globe with similar outcomes.

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Appendix 1. Contributing members of the Canadian Pediatric Neurosurgery Study Group

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