Incidence of Failure in Ventriculoperitoneal and Lumboperitoneal Shunts in Patients with Idiopathic Intracranial Hypertension

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THESIS

Presented to the Department of Public Health and Preventive Medicine

and the Oregon Health & Science University

School of Medicine

In partial fulfillment of

the requirements for the degree of Master of Public Health

November 2012

Department of Public Health and Preventive Medicine

School of Medicine

Oregon Health & Science University

CERTIFICATE OF APPROVAL

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ABSTRACT

Introduction: Idiopathic intracranial hypertension (IIH) is a condition of raised intracranial pressure of unknown cause. Symptoms and signs include headache, pulsatile tinnitus, transient visual obscurations, papilledema, an in severe cases, visual loss and blindness. Lumboperitoneal (LP) and ventriculoperitoneal (VP) shunts are the primary surgical interventions used to treat IIH; however, LP and VP shunts frequently require multiple revisions and have a number of complications. Current information concerning the relative incidence of, and reasons for, failure in LP and VP shunts is poorly understood. **Hypothesis:** We proposed that at two years from first surgery, LP and VP shunts would have different incidences of failure. Additionally, we proposed that independent predictors such as BMI, lumbar opening pressure, and time from initial diagnosis to first surgery would be associated with failure. **Methods:** Using a retrospective cohort design and drawing a sample from the Intracranial Hypertension Registry, we randomly selected 241 subjects using the Modified Dandy Criteria. After excluding for childhood presentation, poor data quality, and lack of follow up (44%), we performed negative binomial regression and Chi-square tests for difference of two proportions. We also constructed Kaplan-Meier curves and performed Log-Rank tests to evaluate differences. **Results:** Our study sample was demographically similar to previous studies and known risk factors, with 96.3% female, 86.3% with BMI >30, and a mean age of 32. The median time-to-failure for first four failures were 125 days, 98 days, 158 days, and 73.5 days, respectively. At two years from initial surgery, we observed a ratio of 1.38 VP shunt failures for every LP shunt failure (95%CI 0.90 – 2.10) p = 0.139. None of our independent variables were associated with failure. Previous optic nerve sheath decompression (ONSD), 0.69 (95% 0.37 – 1.28), 10mmHg increase in diastolic blood pressure above 90mmHg, 1.11 (95%CI 0.98 – 1.25). Visual analysis of Kaplan-Meier plots and the Log Rank testing suggest that survival analysis would be a more appropriate technique to factor in the time component for failure. **Conclusion:** Our study provides limited evidence that LP and VP shunts have different failure rates. Our study has the unique strength of being able to assess the occurrence of shunt failures in a sample drawn from a registry with cases from around the world, and therefore may be generalizable to many locations and medical settings. However, limitations include relatively small sample size and lack of outcome specificity, with all types of failures and revisions combined into a single category. Future studies using data from the IHH Registry will have the benefit of larger sample sizes, as more cases are accrued, allowing the analysis by more specific outcome types.

INTRODUCTION

Background:

Idiopathic intracranial hypertension (IIH) (formerly known as pseudotumor cerebri) is a condition of raised intracranial pressure resulting in headache, tinnitus, blurry vision, papilledema, and in severe cases, significant visual loss and blindness. A diagnosis of exclusion, IIH is defined as cerebral spinal fluid (CSF) pressures greater than 250mmH2O with otherwise normal CSF composition, neuroimaging findings and neurological examination. This is in contrast to secondary intracranial hypertension (SIH) in which an underlying cause (tumor, obstruction, trauma, etc.) can be identified. With clear targets for therapy in patients with SIH, curative treatments are possible. Unfortunately, no such targets exist in patients with IIH, limiting treatment to an often lifelong quest towards symptom relief and prevention of visual loss.

Epidemiology:

Although the cause of IIH remains unclear, several risk factors have been identified, including female sex, child bearing age, and obesity [1-4]. For example, while the baseline incidence of IIH is estimated at 1case per 100,000 people, the incidence increases to 14 cases per 100,000 in obese women, and further increases to 20 cases per 100,000 in obese women of child bearing age (age 20-44) [4]. These incidences are likely underestimates, as many patients with IIH are misdiagnosed as having chronic headaches (the most common chief complaint) [5]. Only 68% of IIH patients report visual disturbances, prompting physicians to check for papilledema, which is critical to making the correct diagnosis [6-9]. The overall prevalence of IIH in the United States is estimated at 25,976 cases, the annual incidence 6,041 new cases, and the average duration of illness approximately 4.3 years. With the number of overweight and obese women continuing to climb [10], the health burden of IIH is expected to increase in the coming decade.

Pathology:

Cerebrospinal fluid (CSF) is a clear, colorless fluid that surrounds and protects the brain and spinal cord from trauma, and assists in the exchange of nutrients and wastes. The slightest

increase in CSF volume, however, can result in significantly elevated intracranial pressures, leading to headache, nausea, tinnitus, blurry vision, and in severe cases, blindness. Increased CSF volume is thought to be due to an imbalance between production from the choroid plexi, and arachnoid granulations absorption into the venous sinuses. This physiologic model serves as the foundation for several hypotheses which attempt to explain the biological mechanism of IIH.

One such hypothesis suggests that IIH may result from high downstream cerebral sinus venous pressures, which slow CSF drainage through arachnoid granulations until enough pressure builds up to create a new steady state. In a study by Higgins et al, 13 of 20 IIH patients displayed bilateral transverse sinus obstruction, compared to 0 of 40 controls [11]. Although cerebral sinus venous hypertension is a frequent finding in patients with IIH, there is no clear single explanation for its presence [12]. One aspect that remains unclear is which comes first, the transverse sinus stenosis or increased CSF pressure. Bono et al attempted to answer this question by reducing CSF pressures in 14 patients with transverse sinus stenosis [13]. All 14 patients continued to have stenosis despite their reduced CSF pressures. While this study shows that transverse sinus stenosis can continue to exist despite a return to normal CSF pressures, it does not answer whether the stenosis occurred before the elevated CSF pressures. Other studies have looked at whether correcting transverse sinus stenosis can improve IIH symptoms. In a study by Higgins et al, 12 IIH patients with transverse sinus stenosis underwent correction of their stenosis. Of these 12 patients, seven showed improvement in IIH symptoms while five remained unchanged [14]. Additional interventional studies will be helpful in determining whether correcting an underlying stenosis results in reduced CSF pressures.

Other biologically plausible mechanisms have focused on the interplay between obesity and IIH. Currently proposed mechanisms include increased cardiac filling pressures produced by increased abdominal pressures in obesity [15], chronic inflammation [16], defects in the hypothalamic-pituitary-adrenal axis [17], and increased serum leptin [18-21]. In summary, as a diagnosis of exclusion, IIH may encompass multiple dysfunctional regulatory processes. This illustrates the concept of multifactorial causes, in which transverse sinus stenosis and elevated leptin would be neither sufficient nor necessary to cause IIH, but may contribute to the overall set of factors capable of leading to the development of IIH. Continued research

into the biologic mechanisms underlying IIH will only further improve treatment options. Until these mechanisms become clearer, however, treatment for IIH will continue to be limited to symptom relief.

Treatment (Medications):

Initial treatment for IIH consists of medical management, primarily with carbonic anhydrase inhibitors such as acetazolamide. Although acetazolamide has FDA approval for use in treating diseases like high altitude sickness, alkalosis, and glaucoma, its use remains off label for IIH. To date, no FDA studies or formal trials have assessed the efficacy of acetazolamide in patients with IIH. In a few case series, Lubow and Kuhr, and Tomask et al observed IIH patients successfully treated with acetazolamide [22-23]. However, in a more recent study, Johnson et al failed to observe significant symptom relief in IIH patients treated with acetazolamide [24].

In addition to its undemonstrated efficacy, acetazolamide also has several setbacks. As a sulfa-related drug, it is not tolerated by all patients, and generally requires physician supervision as patients are started at introductory levels of 250mg and slowly increased to 1000-2000mg daily [25]. Side effects can include kidney stones, metabolic acidosis, and in rare cases, severe aplastic anemia. For patients who cannot handle acetazolamide, other diuretic drugs with CAI activity are attempted. These include neptazane, furosemide, and topiramate [26]. Unfortunately, these drugs also lack formal efficacy trials. For example, while topiramate is thought to prevent papilledema by the similar CAI-like mechanism [27], little evidence currently exists as to whether or not this logic translates into clinical efficacy.

Treatment (Surgery):

When medical intervention fails, or when visual loss seems imminent (which is estimated to occur in approximately one quarter of all IIH patients), surgical treatment becomes necessary [28]. One such surgical option is optic nerve sheath decompression (ONSD). ONSD is the most appropriate immediate procedure when visual loss and blindness are the primary concern [29-31]. In a study by Kelman et al, 17 patients with progressive IIH received ONSD and showed improved visual acuity in 33 of 34 eyes [32]. Interestingly, only 21 of the 34 eyes received ONSD, suggesting that unilateral surgery could improve visual acuity in both eyes.

Alsuhaibani et al observed similar bilateral improvements in visual acuity after unilateral ONSD [33].

When comorbid obesity is a concern, gastric bypass may be a more desirable surgical option. Sugerman et al observed resolution of headache and pulsatile tinnitus at four months post-surgery in 18 of 19 individuals receiving gastric bypass [35,36]. In fact, weight loss in general is thought to improve IIH symptoms, regardless of whether it is obtained through surgical or lifestyle means. For example, in a case series by Newborg, nine obese patients achieved remission of papilledema after weight loss [34]. Another study observed remission of papilledema and blurry vision in patients obtaining 6% weight loss [24].

Although ONSD and weight loss appear to be effective in resolving papilledema, relieving the underlying increase in CSF pressure ultimately requires shunt surgery. Shunts come in two varieties: lumboperitoneal (LP) and ventriculoperitoneal (VP). In LP shunts, CSF is drained from the lumbar cistern, while in VP shunts the fluid is drained from one of the lateral ventricles of the brain. Both shunt types divert the CSF into the peritoneum where it is passively reabsorbed. Because many IIH patients tend to have smaller ventricles, historically, surgeons have preferred LP shunts. With recent advances in stereotaxic techniques, however, use of VP shunts is increasing. Both are very successful at acutely relieving many of the symptoms of IIH [37-44]. In a retrospective study by Burgett et al, 82% of IIH patients receiving LP shunts showed improvements in diplopia, visual obscurations, and tinnitus. Patients receiving VP shunts showed similar improvements. In a separate study by Woodworth et al, of 21 IIH patients receiving stereotaxic VP shunts, 100% showed immediate improvement in headache and egress of CSF [45].

Despite their observed short term efficacy, LP shunts and VP shunts frequently require one or more revisions and have a number of complications. For example, in the same study by Woodworth et al, 10% of VP shunts failed within 3 months, 20% failed by 6 months, and 50% failed by 12 months. Similarly, Rosenberg et al observed that 73 LP shunts and 10 VP shunts were required to treat a sample of only 37 patients, with 64% of shunts failing within six months [43]. Only 14 of the 37 patients retained symptom relief after one shunt procedure. Supporting these findings, another recent retrospective study observed that 67% of patients receiving LP shunts had to undergo an average of 6.35 revisions over a follow-up

period of 6 to 143 months [38]. The average time to revision was approximately 9 months [38,43].

When a shunt fails, the failure is often categorized according to mechanical or biological complications. The most common mechanical complications include valve obstruction, catheter breakage or migration, and over-drainage [46,47]. Over-drainage is an especially common problem, with IIH patients often experiencing hypotensive CSF headaches. Shunt revisions are often required to readjust the CSF flow rate [43]. The advent of programmable valves greatly improved the mechanical control of flow rates. Unfortunately, frequent readjustments still need to be made, since the understanding of the ever shifting human component continues to elude scientists. Biological complications of shunt surgeries can be much more severe, sometimes requiring complete shunt removal as opposed to revision. These complications include infection, abdominal or radicular pain, Chiari II malformation, and hemorrhage. How these mechanical and biological complications compare between LP shunts and VP shunts remains unclear.

Evidence concerning the comparative incidence of failure in LP shunts and VP shunts is also inconclusive. In a study of 42 patients from a single institution, McGirt et al concluded that LP shunt patients had a 2.5 fold (95% CI 1.5- 4.3) increased risk of revision compared to VP shunt patients [48]. Contrary to this finding, however, both Aokin and Wang et al observed a lower incidence of failure in LP shunts compared to VP shunts [46,49].

Even within studies, the failures rates between LP shunts and VP shunts demonstrate inconsistency. In a retrospective chart review, Abubaker et al found that among 25 patients with IIH, LP failure rate was 11% compared to 14% in neuronavigation-assisted VP shunts with programmable valves. With respect to revision, however, Abubaker observed a reverse trend, with a greater number of LP shunts requiring revision (60%) compared to the neuronavigation-assisted VP shunts (30%) [50]. These inconsistent findings suggest a need for further research.

One possible explanation for these inconsistencies is that as of 1999 there were at least 127 commercially available valve devices for VP shunts, with more than 450 pressure ranges and 2,000 assemblies [51]. With so many variations, external consistency may be difficult to obtain when each hospital uses its own unique device or method. But even when the device,

physician, and hospital remains constant, a high degree of variability still exists in the patient to patient failure rates, suggesting that some unaccounted for patient-related factor(s) may be contributing to the inconsistency in findings. For example, Eggenberger et al observed that 53% of VP revisions were tied to a small subset of patients (3 from a total sample of 15) [39]. Attempting to shed light on these possible patient related factors, McGirt et al observed that having an IIH diagnosis more than two years prior to surgery was significantly associated with a reduced likelihood of symptom relief at 6 and 12 months [48]. Other studies have observed increased failure rates in patients lacking papilledema. If patient-related factors are truly associated with shunt failure, identifying these factors could improve the accuracy and precision of studies comparing shunt failure rates, and also help guide attempts at reducing risk factors for failure.

Economics:

Because IIH treatment options are limited to symptom relief, treatment is lifelong. The need for lifelong care presents a large physical and emotional burden for patients, and a substantial financial burden on the healthcare system. In 2009, over $444 million was spent annually treating IIH patients. Hospital admission costs for IIH patients were four times the national average, with approximately $8931 spent annually on admissions per person. This higher inpatient cost per patient is thought to reflect a higher number of admissions [52]. For example, although fewer than 26,000 people are currently diagnosed with IIH, in 2007, more than 9800 hospital admissions were reported for IIH related illness [52]. Shunt surgeries and revisions comprise a large component of admissions and spending, with approximately 1969 procedures per year costing over $60 million annually.

Summary:

Despite limited information on the effectiveness and predictors of failure for VP shunts and LP shunts, both procedures continue to be frequently used as treatments for IIH [53]. Additionally, choice of shunt appears to be based on surgeon expertise as opposed to evidence of clinical efficacy. Without accurate, reliable, and precise scientific information on the comparative effectiveness and correlates for failure in VP shunts and LP shunts, little can be done to improve symptom relief and treatment options for patients with IIH. In our study, we measured the incidence of failure in VP and LP shunts and assessed pre-surgical patient

factors for their association with shunt failure. Specifically, we hypothesized that LP and VP shunts would have different failure rates at two years, and that among pre-surgical patient factors, lumbar pressure, body mass index (BMI), and time from initial diagnosis to initial surgery would all be associated with shunt failure.

METHODS

Design:

We used a retrospective cohort study design, with subjects retrospectively selected according to exposure (VP or LP shunt) and followed forward in time to assess for failure. We chose two years of follow up time in order to balance the need to obtain a sufficient amount of time to detect a difference in failure rates with the need for a sufficiently large sample size. Our primary outcome (number of failures at two years) was measured by summing the number of revision surgeries listed in the medical record occurring within two years the initial surgery date.

Study Population:

Our study population came from the Intracranial Hypertension Registry (IHR). The IHR is the largest international database of patients with intracranial hypertension in the world, consisting of 1617 enrolled patients from 24 countries, and is jointly sponsored by the Intracranial Hypertension Research Foundation (IHRF) and the Casey Eye Institute at Oregon Health and Science University. The Registry is approximately 30% physician referral and 70% self-referral. To enter the Registry, adult patients must complete an initial questionnaire, which includes consent and authorization for the IHR to obtain and use pertinent medical information for research purposes. Trained registry-staff then evaluate the patient's medical records and a volunteer physician verifies a diagnosis of intracranial hypertension.

Inclusion Criteria:

We obtained our study sample by randomly selecting from Registry medical records, for patients with a confirmed diagnosis of IIH, an initial VP or LP shunt surgery occurring after IIH diagnosis, and no prior history of Secondary Intracranial Hypertension or shunt surgery.

We used the following modified Dandy Criteria (Figure 1) to confirm IIH diagnosis. We ensured that all shunt surgeries listed in the medical record had accurate information regarding shunt type and date. Whenever possible, we also verified IIH as the primary reason for surgery. Altogether, we obtained a sample of 212 patients, 72 with VP shunts and 140 with LP shunts.

Figure 1. Modified Dandy Criteria

- Signs and symptoms of increased intracranial pressure (eg, headache, blurred vision, tinnitus, papilledema, visual defects, etc)
- No localizing findings on neurologic exam
- Normal MRI/CT scan with no evidence of venous obstructive disease
- Opening CSF pressure: > 250 mmH_2O with normal CSF constituents
- Awake and alert patient
- No known cause of increased intracranial pressure found

Exclusion Criteria:

From our initial sample of 212, we excluded a total of 77 subjects (37%). We excluded 18 (8%) due to poor quality of information, which we defined as multiple missing surgery dates and/or surgery dates rounded to the nearest year. Including these individuals would have underestimated failure rates, and more so for the LP group, as there was a disproportionately higher percentage of poor data quality in the LP group (13 of 140 LP, compared to 4 of 72 VP). We excluded 44 (21%) for having less than two years of follow up time (those with initial surgeries after November 1, 2007). Including these individuals would have biased selection towards subjects with the shortest times to failure, thus overestimating failure rates, and differentially towards those with VP shunts, as more patients with VP shunts had entered the registry after November 2007. Finally, we excluded 15 (8%) for childhood presentation, based on the idea that continued body growth in children might create a uniquely different set of issues influencing LP and VP failure rates. With the vast majority of IIH occurring in adults, we were willing to limit our generalizability in an effort to maintain stronger internal validity.

Data Collection:

Using a pilot-tested data abstraction form, we collected information on additional patient and surgical variables. We modeled our abstraction form after previously validated forms used by the IHRF, and tested for inter and intra researcher agreement, which yielded high validity. We collected information on age, gender, body mass index (BMI), lumbar puncture opening pressure, date of IIH diagnosis, biological or mechanical categorization of shunt failures, optic nerve sheath decompression (ONSD) date, gastric bypass date, systolic blood pressure, diastolic blood pressure, hypertension, diabetes mellitus, and dose and frequency of acetazolamide, topiramate, neptazane, and furosemide. To ensure appropriate temporality between predictor and outcome, all predictor values corresponded to measurements reported prior to initial shunt surgery. For variables with multiple entries (lumbar opening pressure, blood pressure, BMI) we used the maximum value occurring before initial shunt surgery, in an attempt to standardize patients according to their most severe "pre-treatment" values.

We also extracted information on specific mechanical and biological reasons for shunt failure. Mechanical reasons included peritoneal catheter malfunction, over-drainage, valve obstruction, and failure due to other mechanical reasons. Biological reasons included subdural hemorrhage, subarachnoid hemorrhage, intra-cerebral hematoma, visual loss from retinal ischemia, acquired Chiari II malformation, intracranial aneurysm, infection, and failure due to other biological factors.

Statistical Analysis:

All statistical analyses were performed using STATA 11.0.

Variable Classification:

Predictor variables were classified as continuous or categorical based on classifications observed in previous studies (i.e. Body Mass Index (categorical): overweight (25-30), obese (30-40), morbidly obese (40+)). We ensured normal distribution for continuous variables, using histogram analysis, and performed scatter plot analyses to assess for visually consistent relationships with time to failure (Appendix A, Figure A1).

We used two different classifications for our outcome variable; time to failure (continuous), and number of failures occurring at two years from first surgery (discrete). Time to failure was defined as the interval t(i – (i-1)), where i=date of current failure, and (i-1) = date of previous failure. This definition was used to prevent previous failure times from carrying over into measurements for subsequent failures. We also made sure that previous failures were not actually predictive of subsequent failures, by assessing scatter plots and performing linear regression (Appendix A, Figure A2, Table A3). To obtain a sufficient number of observations in failures 2-4, we allowed for follow up time beyond two years.

Descriptive Statistics:

We ran tab summaries for predictor variables both by total sample and by shunt type. To check for potential associations we performed a two-sided student t-test for a difference of means on our continuous variables, and either a Chi-Square test for a difference in proportional trends or a Fishers test (variables with <5 observations in >20% of categories) on categorical variables. We tabulated counts and percentages for mechanical and biological reasons for failure, and performed Fisher's exact tests to determine whether failure reasons for failures 1-3 differed by shunt type.

Finally, we performed descriptive statistics on the mean time to first, second, and third failures both by total sample and by shunt type. (For this specific test, we used accumulated time from first surgery as opposed to time from previous failure). This test allowed us to compare time to failure against measurements observed in other studies.

Kaplan Meier and Simple Log Rank Test:

We performed Kaplan Meier and Simple Log Rank Tests for Survival Equality for failures 1-4, this time using time from previous failure as the measurement of our failure outcome. From these tests, we obtained information on visual trends for the purpose of generating future hypotheses for survival analysis testing.

Negative Binomial Analysis and Final Model Building:

Finally, we used univariate and multivariate Negative Binomial Regression to test our hypothesis. We chose Negative Binomial Regression based on an observed lack of Poisson distribution in our predictor variables (Appendix A, Table A4). Specifically, predictor

variables had variances greater than their respective means, as observed by a statistically significant over-dispersion factor using a likelihood ratio test. Each of our analyses obtained significant likelihood ratio tests for over-dispersion of means ($p < 0.050$).

Using multivariate regression, we built a final model to predict the number of failures occurring within two years of initial surgery. Using a cutoff of $p<0.25$ from univariate association, we applied a forward building method, incorporating additional predictor variables one at a time, starting with those variables with the smallest p-values. We kept variables in our final model if they continued to show a trend towards association ($p < 0.25$).

RESULTS

Descriptive Statistics:

Baseline characteristics were similar in patients receiving VP and LP shunts. As presented in Table 1, the mean age of our total sample was approximately 32 years, the mean lumbar opening pressure for the total sample was 407 mmH2O, and the mean systolic and diastolic blood pressures were 137 mmHg and 86 mmHg respectively.

Table 1. Descriptive Statistics: Medians, Means, and 95% CI for Continuous Variables by Total Sample and Shunt Type

	Total		LP shunts		VP shunts		*p-value
	mean	median	mean(95%CI)	median	mean(95%CI)	median	
age	32	31	32 (30.0 - 33.3)	32	32 (29.6 - 34.6)	31	0.77
lumbar	407	380	403 (380.1 - 426)	380	417 (382.4 - 451.1)	415	0.51
systolic	137	138	137 (132 - 141.3)	139	138 (127.3 -148.4)	138	0.80
diastolic	86	86	84 (81.2 - 87.5)	86	88 (81.9 - 94.4)	84	0.22

*Student t-test

As observed in previous studies of IIH patients, the vast majority were female (96.3 %) compared to male (3.7%), and had a BMI>30 (86.3%) (Table 2). Approximately 50% had received their first shunt surgery within two years of IIH diagnosis, and 19% had previously received ONSD. Using a chi-squared test (Fisher's exact test if >20% of expected frequencies <5) none of our categorical variables were associated with surgery type. Time from IIH diagnosis to first surgery trended towards significance (Fisher's exact p= 0.21) with more LP

shunts placed within two years of initial IIH diagnosis (60.0%) compared to VP shunts (25.0%).

Table 2. Descriptive Statistics: Frequencies and Percentages of Categorical Variables by Total Sample and Shunt Type

		Total		LP shunts		VP shunts		p-value
		Frequency	Percent	Frequency	Percent	Frequency	Percent	
Sex	Male	5	3.7	5	5.4	0	0	*0.33
	Female	129	96.3	87	94.6	42	100	
BMI	<25	6	7.2	5	8.3	1	4.4	*0.38
	25-30	5	6.0	5	8.3	0	0	
	30-40	36	43.4	24	40.0	12	52.2	
	40-50	30	36.1	23	38.3	7	30.4	
	>50	6	7.2	3	5.0	3	13.0	
ONSD	yes	25	18.7	19	20.7	6	14.3	+0.38
	no	109	81.3	73	79.4	36	85.7	
Diagnosis	<2years	14	50.0	12	60.0	2	25.0	*0.21
	>2years	14	50.0	8	40.0	6	75.0	

*Fisher's exact test, + chi-squared test

The reasons for shunt failure are presented in Table 3. Subtypes of mechanical and biological failure were noted for both shunt types.

Table 3. Descriptive Statistics: Failure Reason (General and Subtype) for First Three Failures by Shunt Type

		LP shunt				VP Shunt			
Failure Type:		1st	2nd	3rd	Total (avg)	1st	2nd	3rd	Total (avg)
Mechanical	Peritoneal	12 (37.5)	7 (33.3)	4 (28.6)	23 (34.3)	4 (23.5)	2 (28.3)	2 (20.0)	8 (23.5)
	Obstruction	4 (12.5)	4 (19.1)	1 (7.1)	9 (13.4)	6 (35.4)	1 (14.3)	2 (20.0)	9 (26.5)
	Over-Drainage	9 (28.1)	3 (14.3)	0 (0)	12 (17.9)	0 (0)	0 (0)	2 (20.0)	2 (5.9)
	Other	3 (9.4)	3 (14.3)	3 (21.4)	9 (13.4)	3 (17.7)	2 (28.6)	1 (10.0)	6 (17.7)
	Total	28 (87.5)	17 (90.0)	8 (57.1)	53 (79.1)	13 (76.5)	5 (71.4)	7 (70.0)	25 (73.5)
Biological	Infection	0 (0)	3 (14.3)	3 (21.4)	6 (9.0)	3 (17.7)	1 (14.3)	2 (20.0)	6 (17.7)

Other	4 (13.0)	1 (4.8)	3 (21.4)	8 (11.9)	1 (5.9)	1 (14.3)	1 (10.0)	3 (8.8)
Total	4(13.0)	4 (19.1)	6 (42.9)	14 (20.9)	4 (23.3)	2 (28.6)	3 (30.0)	9 (26.5)
Fishers (subtype)	0.006	0.86	0.61					
Fishers (general)	0.70	0.62	0.68					

Averaging reasons for top four reasons for failures, mechanical failures account for 79.1% of LP shunt failures and 73.5% of VP shunt failures, while biological reasons account for 20.9% and 26.5% respectively. For LP shunts, the three major reasons for failure are Peritoneal (34.3%), Over-Drainage (17.9%) and both obstructive and other mechanical, each at 13.4%. For VP shunts, the three major reasons for failure are Obstruction (26.5%), Peritoneal (23.5%) and both infection and other mechanical (17.6% each). While over-drainage is the second most common reason for LP shunts, is it not within the top three for VP shunts. Similarly, obstruction and infection both appear to account for a greater percentage of VP shunt failures than LP shunt failures. Most of this difference stems from reason for first failure, with Fisher's exact test for difference in subtypes (p =0.006).

In our total sample, mean time to first failure was 310.9 days (10.4 months) with a median of 125 days (Table 4). For LP shunts, the mean time to first failure was 372.2 days (12.4 months), with a median of 168.5 days indicating a right-skewed distribution; while in the VP group, the mean was 176.1 days (5.9 months) with a median of 96.5 days.

Table 4. Median and Mean Times to Failures 1-4 in Total Sample and by Shunt Type

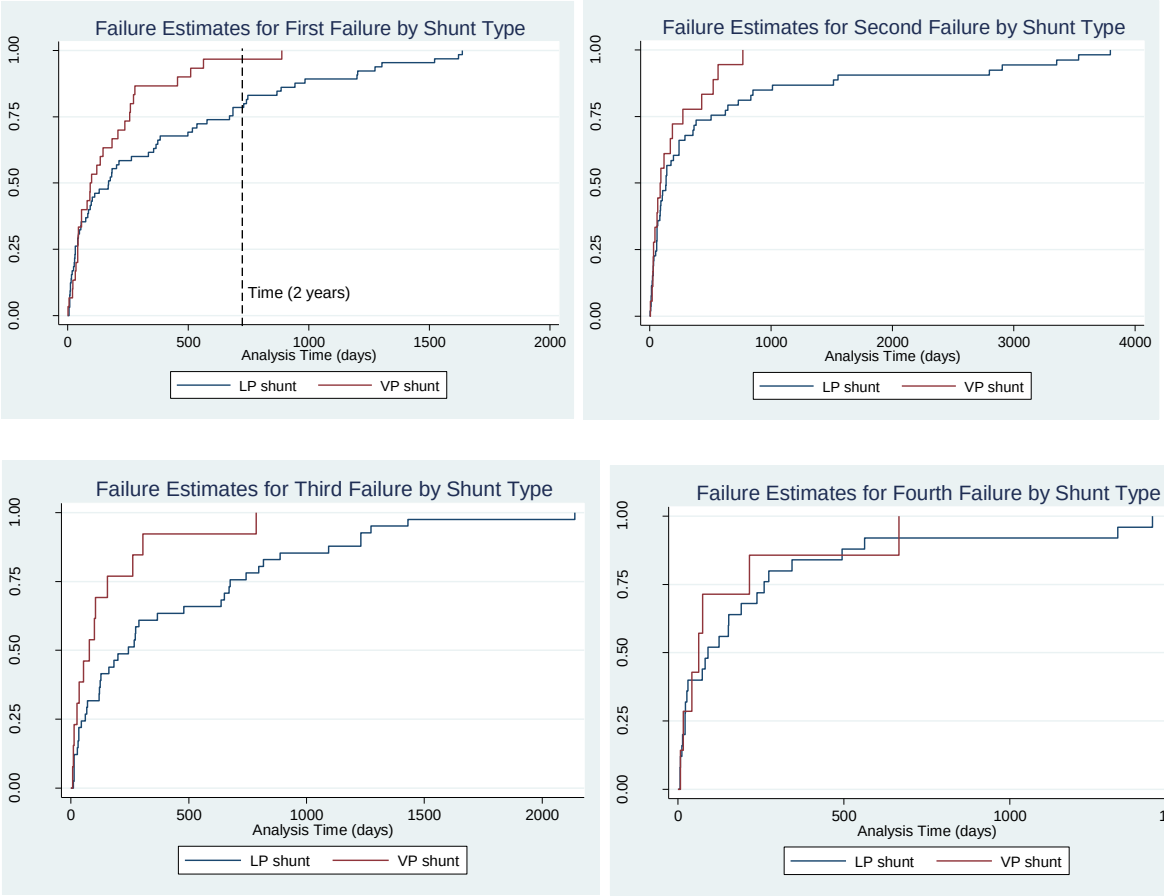
	Failure 1 (n=96)		Failure2 (n= 76)	
	Median	Mean (95%CI)	Median	Mean (95% CI)
Total	125	310.9	98	427.8
LP Shunt	168.5	372.2 (260.8 - 483.5)	119	518.34 (265.4 - 771.3)
VP Shunt	96.5	176.1 (101.2 - 251)	75.5	174.25 (70.6 - 277.9)
	Failure3 (n=54)		Failure 4 (n=34)	
Total	158	368.2	73.5	207.2
LP shunt	244	437.7 (280.6 -594.7)	86.5	229.3 (79.6 - 379.1)
VP shunt	78	148.9 (19.9 -278)	52	135.4 (-52.9 - 323.6)

Kaplan Meier and Log Rank Testing:

Using a Kaplan-Meier analysis plot (Figure 5), we observed a visual similarity in failure rates between LP and VP shunts within the first 100 days of placement. However, after 100 days, VP shunts appeared to fail at a faster rate. 100% of VP failures occurred by

approximately 900 days, compared to only 80% of LP shunts. At two years, approximately 25% of LP shunts were patent compared to 5% of VP shunts. Similar patterns were visualized for the second to fourth failures.

Figure 5. Kaplan-Meier Failure Estimates by Shunt Type (Failures 1-4)



Using the time intervals from Kaplan-Meier analysis, we performed simple log rank tests for equality in survivor functions (Table 6). For first failure, observed LP shunt failures were significantly less than expected (65.0 versus 73.7, p= 0.03) while observed VP shunt failures were significantly greater than expected (30.0 versus 21.3). For second and third failure, log rank testing trended toward or achieved significance, with a similar pattern of observed versus expected failures.

Table 6. Log Rank Test for Equality of Survivor Functions by Surgery Type (Failures 1-4)

		observed	expected	p-value
Failure 1	LP shunt	65.0	73.7	0.03
	VP shunt	30.0	21.3	
Failure 2	LP shunt	53.0	57.8	0.13
	VP shunt	18.0	13.2	
Failure 3	LP shunt	41.0	47.1	0.010
	VP shunt	13.0	6.9	
Failure 4	LP shunt	25.0	26.1	0.61
	VP shunt	7.0	5.9	

Hypothesis Analysis:

IIH patients experienced a mean of 1.35 shunt failures within two years of first surgery, with 1.23 failures for LP shunts and 1.62 failures for VP shunts (Table 7). Patients with BMI <25 had a mean of 0.83 failures at two years, increasing to 2.03 failures in patients with BMI 40-50, but then declining to 1.00 failures in those with BMI >50. Those with a prior history of ONSD had a mean of 0.84 failures at two years, while those without previous ONSD had 1.47 failures. Lastly, patients receiving shunt surgery within two years of diagnosis had a mean of 1.50 failures at two years, while those waiting more than two years before surgery had 1.43 failures.

Table 7. Failures Occurring within Two Years of First Surgery for Categorical Predictor Variables

Predictor Variable:		Number of Failure at Two Years		
		Mean	SD	Variance
Total Sample		1.35	1.49	2.23
Shunt Type	LP	1.23	1.41	1.98
	VP	1.62	1.65	2.73
BMI	<25	0.83	1.60	2.57
	25-30	1.00	1.41	2.00
	30-40	1.25	1.52	2.31
	40-50	2.03	1.73	3.00
	>50	1.00	0.89	0.80
ONSD	yes	0.84	0.94	0.89
	no	1.47	1.57	2.47
Diagnosis	< 2years	1.50	1.51	2.27
	> 2years	1.43	1.55	2.42

Univariate Negative Binomial Regression:

Using univariate negative binomial regression (Table 8), we observed no difference between LP and VP shunt failures at two years from first surgery, with an estimated 1.30 VP shunt failures (95% CI 0.87 –1.94) for every LP shunt failure (p = 0.203). Applying univariate negative binomial regression to our other predictor variables (Table 9), we observed no statistically significant associations. Previous ONSD trended towards statistical significance (p<0.10). Those with previous ONSD had 0.57 times the rate of shunt failure (95% CI 0.32 - 0.99, p =0.86) compared to those without.

Table 8. Univariate Negative Binomial Regression (Incidence Rate Ratios) for Number of Failures at Two Years by Shunt Type

	Overdispersion	Constant	Coefficient	Incidence Rate	p-value
LP	-	-	-	-	-
VP shunt	*0.55 (0.28 - 1.06)	0.22 (-0.01 - 0.46)	0.26 (-0.14 - 0.66)	1.30 (0.87 – 1.94)	0.203

*Likelihood-ratio test of alpha=0 p<0.001

Incorporation of term for over dispersion (alpha), is significant (p =0.000) suggesting model has over dispersed variances compared to means. Under this negative binomial assumption, VP shunts have an estimated 1.30 failures (95%CI 0.87 – 1.94 failures) for every LP shunt failure (p= 0.203).

Table 9. Univariate Negative Binomial Regression Predicting Number of Failures Occurring Within Two Years of Surgery

		Over-dispersion	Constant (Bo)	variable coefficient (B1)	incidence rate	*p-value
age		0.56 (0.29 - 1.09)	0.66 (-0.13 - 1.44)	(-)0.11 (-0.36 - 0.13)	0.89 (0.70 - 1.14)	0.361
lumbar		0.66 (0.35 - 1.26)	0.09 (-0.75 - 0.92)	1.33 (-3.58 - 6.23)	3.76 (0.03 - 509.76)	0.597
systolic		0.48 (0.22 - 1.08)	0.03 (-1.13 - 1.18)	0.03 (-0.06 - 0.11)	1.02 (0.94 - 1.11)	0.566
Diastolic BP	<90	-	-	-	-	-
	90-100	0.43 (0.19 – 1.00)	0.26 (-0.01 – 0.53)	0.29 (-0.18 – 0.75)	1.33 (0.84 – 2.12)	0.228
	>100	0.43 (0.19 – 1.00)	0.26 (-0.01 – 0.53)	0.21 (-0.41 – 0.83)	1.24 (0.66 – 2.29)	0.502
BMI	<25	-	-	-	-	-
	25 - 30	0.53 (0.22 - 1.27)	(-)0.18 (-1.23 - 0.87)	0.18 (-1.33 - 1.69)	1.20 (0.26 - 5.43)	0.813
	30 - 40	0.53 (0.22 - 1.27)	(-)0.18 (-1.23 - 0.87)	0.41 (-0.71 - 1.52)	1.50 (0.49 - 4.59)	0.477
	40 - 50	0.53 (0.22 - 1.27)	(-)0.18 (-1.23 - 0.87)	0.89 (-0.22 - 2.00)	2.44 (0.80 - 7.43)	0.116
	>50	0.53 (0.22 - 1.27)	(-)0.18 (-1.23 - 0.87)	0.18 (-1.26 - 1.62)	1.20 (0.28 - 5.09)	0.805
ONSD	no	-	-	-	-	-
	yes	0.52 (0.26 - 1.04)	0.38 (0.18 - 0.59)	(-)0.46 (-0.99 - 0.06)	0.57 (0.32 - 0.99)	0.086

Diagnosis	<2 years	-	-	-	-	-
	>2 years	0.48 (0.10 - 2.26)	0.41 (-0.16 - 0.97)	(-) 0.05 (-0.85 - 0.75)	0.95 (0.43 - 2.11)	0.905

*p-values for predictor coefficients

In univariate negative binomial regression for continuous and categorical predictor variables, each variable displayed a significant likelihood ratio for over-dispersion factor alpha. Among continuous variables, only diastolic blood pressure was significant in increasing the risk of failure, with 1.13 times the incidence of failure expected for every 10mmH2O increase in diastolic blood pressure (p =0.050). Among categorical variables, previous ONSD surgery was significantly associated with a decreased risk of failure. Those with previous ONSD had 0.57 times the rate of failure compared to those never receiving previous ONSD (p=0.048). For other variables, notably BMI, incidence rate point estimates were consistently >1, however, confidence intervals were wide, incorporating the null value for every group.

Multivariate Negative Binomial Regression:

Finally, we performed multivariate negative binomial regression (Table 10). Under this final model, none of our variables achieved a statistical association with number of failures occurring at two years. VP shunts had 1.38 times the number of failures at two years (95% CI 0.90 – 2.10) compared to LP shunts, (p = 0.139). For every 10mmHg unit increase above 90mmHg in diastolic blood pressure, we observed 1.11 times the number of failures at two years (95% CI 0.98 -1.25, p = 0.105). Previous ONSD continued to show a protective trend. Those with previous ONSD had 0.69 times the number of failures at two years compared to those without ONSD (95% CI 0.37 – 1.28, p = 0.237). All other variables were neither independently associated with failure rate, nor confounding for predictor variables included in the final model.

Table 10. Final Model from Multivariate Negative Binomial Regression

Number of Failures at 2yrs

=exp(-0.05)* exp (0.322*(VP shunt)) * exp(0.104 *(diastolic BP-80/10)) * exp (-0.37*(previous ONSD))

DISCUSSION

Our study observed a trend toward higher failure rates in VP shunts compared to LP shunts. To determine whether we can expand this observed trend to inferences of causation, we will consider alternative explanations, strengths and weaknesses of our study, and conclude with a discussion of future studies.

Alternative Explanations:

We ensured appropriate temporality by making sure that exposure to VP or LP shunt surgery occurred before failure. Additionally, we ensured that all predictor variables were measured prior to first surgery. With respect to misclassification bias, it is possible that shunts actually failed sooner than our estimates, because we used subsequent surgery dates as an indirect measure of failure. If one type of shunt was associated with a greater delay between failure and revision surgery, this also could have created differential outcome misclassification bias. This bias appeared to be minimal, however, as our estimates of time to failure were similar to those obtained in previous studies. Although we were unable to control for the accuracy or precision of data initially entered into the medical records by surgeons, our own abstraction process yielded high intra- and inter-researcher agreement. Assuming that any residual misclassification bias was non-differential, this would have only served to underestimate the true difference in failure rates.

Because our study population consisted of 70% self-referrals, it is possible that we selected for the most frustrated patients with the poorest outcomes, which would overestimate failure rates compared to the general population. Our failure rates, however, were similar to those observed in other studies that did not use a self-referral population base. Additionally, the baseline demographics of our study sample were similar to those in previous studies. Given these similarities in both failure rates and baseline characteristics, it is unlikely that patients with poorer outcomes of one particular shunt type differentially sought out entry into our study population.

To minimize sample selection bias, we used the objective Modified Dandy Criteria as our inclusion criterion and required a standardized follow up time to prevent loss to follow-up. Unfortunately, in minimizing potential selection bias, we greatly reduced the power of our study. We felt it was more important to minimize selection bias even if it meant reducing the power of our study, because even if the resulting confidence intervals were wide and included the null value, we could have more confidence in the accuracy of our point estimate.

With respect to potential confounding, we did not observe any association between our independent variables and shunt type, with the exception of time from diagnosis to first

surgery. We also adjusted for potential confounding through multivariate analysis. This variable had been proposed in other studies as being significantly associated with shunt failure, although it did not appear to be associated with time to failure in our univariate analysis. Unfortunately, we did not have a sufficient sample size to include time from diagnosis to first surgery in our multivariate analysis (n=32), which raises questions of potential confounding.

We were also unable to assess potential confounding of pharmaceutical interventions, because the drugs, dosing, and frequency regimens changed so often that it was impossible to determine any clear method of measurement that could be applied accurately. While it remains possible that drugs or other variables may contribute unmeasured confounding, these factors would not only need to be associated with failure, but also differentially associated with shunt type. Given what we observed as an often random and exhaustive attempt to try every medication prior to surgery, it seems unlikely that any particular medication or regimen would be differentially associated with one particular shunt type.

We observed a trend towards higher failure rates in VP shunts compared to LP shunts, however, the association did not achieve statistical significance to rule out the role of chance. Two major factors contributed to the increased role of chance. First, our sample size was small. Our initial power estimates demanded a sample size of 80 VP shunts and 220 LP shunts in order to obtain an 80% chance of detecting a difference if it truly existed. Our actual study sample consisted of 42 VP and 93 LP shunts for a total sample size of 135. Variances were also consistently greater than their respective means, implying that failure rates vary considerably from individual to individual. This is concerning, because it indicates that even if a true difference exists between the population-based failure rates in LP and VP shunts, it would be difficult to predict failure rates for the individual with any precision. We thought that some of this variance may be due to a cohort effect, however, we observed no difference in the failure rates of more recent entries compared to older entries. Previous studies of failure rates also show little to no difference over the previous two decades.

Measure of Association:

At two years from first surgery, we observed a ratio of 1.38 VP shunt failures for every LP failure (95%CI 0.90 – 2.10). Although the strength of this association was moderate, the precision was weak as indicated by wide confidence intervals. This lack of precision was likely due a combination of small sample size, and a high degree of legitimate variance in failure rates between individuals. The association was specific with respect to shunt type, but lacked specificity in outcome. To account for this lack of outcome specificity, we ran descriptive statistics on more specific reasons for failure (mechanical, biological, etc). When we looked at mechanical and biological failures, and subtypes within each of these categories, we did not see a difference between VP and LP shunts, with the exception of over-drainage. LP shunts appeared to be more commonly associated with over-drainage compared to VP shunts. With LP shunts taking longer to fail on average, we wondered if over-drainage failures took longer to develop. In a scatter plot analysis, this did not appear to be the case (data not shown). Internal consistency, which we evaluated visually using Kaplan-Meier analysis, showed consistently higher failure rates for VP shunts across multiple failures. With respect to external consistency, the strength of our association was similar to those observed in other studies.

There was clear biologic plausibility for causation, since we were observing the mechanical and biological failing of shunts. Due to the all-or-none nature of our exposure, we were unable to assess a dose-response relationship. We did, however, visually observe that previous shunt failures did not appear to predict times to subsequent failures. Finally, our study did not assess for differences in failure rates within individuals who switched from one shunt type to another.

Strengths and Limitations:

One of the biggest limitations in our study was sample size. To prevent differential misclassification bias and selection bias, we took a conservative approach and excluded a large percentage of our study sample, the majority of which were excluded for lack of follow-up time. To gain some insight into just how much our failure rates would have been skewed

by including patients with lack of follow up, we compared VP and LP shunt failure rates in patients with full follow up and lack of follow up (Table 11).

Table 11. Mean Days to Shunt Revision in Patients with Full and Incomplete Follow Up

	Full Follow-Up		**< 2 Years Follow-up**	
	Days to revision	95% CI	Days to revision	95% CI
VPS	242	146 – 338	101	66 – 136
LPS	343	262 – 424	146	37 - 256

In both LP and VP shunts, the average time to revision occurred sooner in the group with lack of follow-up. Had we included these individuals, we would have reduced the time to failure in VP shunts by 8.3%, but only 4.4% for LP shunts, introducing differential selection bias. By excluding these individuals, we protected our study from this differential selection bias, however, the resulting lack of power may have prevented our study from detecting associations between shunt type and shunt failure as well as associations with other independent variables such as lumbar opening pressures or BMI.

We also measured failure indirectly as the date of subsequent surgery, thus effectively combining failures and revisions into a single category. With previous studies suggesting varying associations between shunt type and revision compared to shunt type and symptom relief, it is possible our lack of association resulted from combining these two different methods of measuring failure. Additionally, while failing shunts almost certainly do not provide symptom relief, functioning shunts may also fail to provide symptom relief. In this respect our study may be geared more towards the interests of surgeons than patients, and our study cannot make inferences on which shunt type provides better symptom relief.

With our measurements, we performed negative binomial regression, however, given the visual trends observed in our Kaplan-Meier analysis, survival analysis may be a more appropriate method for analyzing VP and LP failure rates.

Finally, we attempted to compare our findings to failure rates published worldwide for VP or LP shunts, and discovered that there are hundreds of various models and methods. It may be possible that a particular type of VP or LP shunt works considerably better or worse than another model. For example, with the recent advances in VP shunt technology, neurosurgeons who once hesitated to perform VP procedures may now be more inclined to opt for surgery and revision. While studies comparing specific shunt types would certainly improve exposure specificity and help generate data on the most effective models and techniques, our study wanted to assess the overall burden of shunt failure.

Our study also had some unique strengths. We were able to utilize the largest IIH database in the world in the Intracranial Hypertension Registry. Most shunt studies take place within a single center, sometimes including a few other collaborative surgery practices. In these other studies, the findings can be heavily weighted by surgeon skill and instrumentation. In this way, the findings may not be generalizable, and may demonstrate significantly different results from site to site, creating the uncertainty in failure rates we currently see in the literature. In using a worldwide study population from multiple centers, our study had the ability to characterize the larger status of failure rates in VP and LP shunts, factoring in a variety of devices and surgical abilities.

Future Studies:

Our study attempted to compare failure rates between LP and VP shunts, in an effort to provide physicians and patients with improved information regarding choice of surgery. It is important to recognize, however, that failure rate is only one part of several key issues needed to make a truly informed decision. For example, our study did not assess whether LP or VP shunts differed in terms of symptom relief. Although we observed a higher failure rate in VP shunts, if VP shunts are superior at providing symptom relief, VP shunts may still be the more desirable treatment, despite requiring more frequent revisions.

Another important factor to consider is complication severity. Shunt complications may range from mild to life-threatening, therefore, even if one shunt type requires more frequent revisions, if the complications were more often life threatening, it would make sense to use the less efficient shunt for the sake of reducing debilitating or deadly complications. Although

we observed similarities in mechanical and biological reasons for failure, both shunts had a large proportion of "other" failures. We cannot be sure that all failures within this "other" subgroup are created equal. Additional studies may want to clarify the severity of complications associated with shunt failure.

Finally, we would suggest that the high failure rates observed in both VP and LP shunts may actually be due to problems at the peritoneal end. In our descriptive analysis of reasons for failure, we observed that peritoneal catheter obstruction was one of the most common reasons for failure, suggesting that perhaps the major reason for shunt failure is not necessarily related to LP or VP placement, but rather to faults in the common abdominal exit point. If this is true, improving the peritoneal aspect of VP and LP shunts might show a significant reduction in overall failure rates. Additionally, this common failing at the peritoneal end may be masking the more subtle differences in failures related to VP and LP placement. Given this observation, future studies of VP and LP failure rates may want to exclude peritoneal problems in an attempt to compare failures only due to problems associated with proximal placement.

Summary:

While additional studies may assist in strengthening the case for causation, our study gives moderate evidence that within the first two years, VP shunts trend towards higher failure rates than LP shunts. A larger study design with the ability to assess time from diagnosis to first surgery and pharmaceutical interventions would be helpful in alleviating issues of precision and potential confounding. A study using survival analysis methods may be more appropriate for comparing failure rates and may provide additional information. An interventional study looking at failure rates in patients who switch surgery type would supplement the case for causation.

REFERENCES

1. Balcer, L. J. , Liu, G. T., Forman, S., Pun, K., Volpe, N. J., Galetta, S. L., et al. (1999). Idiopathic intrcranial hypertension: relation to age and obesity in children. *Neurology,* 52, 870-872.

2. Gordon, K. (1997). Pediatric pseudotumor cerebri: Descriptive Epidemiology. *Canadian Journal of Neurological Sciences, 24*, 219 – 221.

3. Digre, K. B., & Corbett, J. J., (2001) Idiopathic intracranial hypertension (pseudotumor cerebri): A reappraisal. *The Neurologist*, 7, 2-67.

4. Durcan, F.J., Corbett, J.J., & Wall, M. (1988). The incidence of pseudotumor cerebri: Population studies in Iowa and Luisiana. *Archives of Neurology*, 45, 875-877.

5. Dhungana S, Sharrack B, Woodroofe N. Idiopathic Intracranial Hypertension. Acta Neurol Scand. 2010 Feb;121(2):71-82. Epub 2009 Nov 23. Review.

6. Wall M. The headache profile of idiopathic intracranial hypertension. Cephalalgia 2002;10:331–5.

7. Radhakrishnan K, Ahlskog E, Cross SA, Kurland LT, Fallon WM. Idiopathic intracranial hypertension (pseudotumor cerebri): descriptive epidemiology in Rochester, Minnesota 1976–1990. Arch Neurol 1993;50: 78–80.

8. Wall M, George D. Idiopathic intracranial hypertension (pseudotumour cerebri), a prospective study of 50 patients. Brain 1991;114:155–80.

9. Wang SJ, Silberstein SD, Patterson S, Young WB. Idiopathic intracranial hypertension without papilloedema. A case control study in a headache centre. Neurology 1998;51:245–9.

10. CDC. Prevalence of overweight, obesity, and extreme obesity among adults: United States, Trends 1976–80 through 2005–2006. Hyattsville, MD: US Department of Health and Human Services, National Center for Health Statistics, CDC; 2008.

11. Higgins JN, Gillard JH, Owler BK, Harkness K, Pickard JD. MR venography in idiopathic intracranial hypertension: unappreciated and misunderstood. J Neurol Neurosurg Psychiatry 2004;75:621–5

12. Karahalios DG, Rekate HL, Khayata MH, Apostolides PJ. (1996). Elevated intracranial venous pressure as a universal mechanism in pseudotumor cerebri of varying etiologies. *Neurology,* 46:198-202.

13. Bono F, Giliberto C, Mastrandrea C et al. Transverse sinus stenoses persist after normalization of the CSF pressure in IIH. Neurology 2005;65:1090–3.

14. Higgins JN, Cousins C, Owler BK, Sarkies N, Pickard JD. Idiopathic intracranial hypertension: 12 cases treated by venous sinus stenting. J Neurol Neurosurg Psychiatry 2003;74:1662–6

15. Sugerman HJ, DeMaria EJ, Felton WL, Nakatsuka M, Sismanis A. Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumor cerebri. Neurology 1997;49:507–11.

16. Sinclair AJ, Ball AK, Burdon MA et al. Exploring the pathogenesis of IIH: an inflammatory perspective. J Neuroimmunol 2008;201–202:202–20.

17. Zada G, Tirosh A, Kaiser UB, Laws ER, Woodmansee WW. Cushing's disease and Idiopathic Intracranial Hypertension: case report and review of underlying pathophysiological mechanisms. J Clin Endocrinol Metab. 2010 Nov:95(11):4850-4

18. Lyon CJ, Law RE, Hsueh WA. Minireview: adiposity, inflammation and atherogenesis. Endocrinology 2003; 144:2195–200.

19. Lampl Y, Eshel R, Kessler A. Serum leptin level in women with idiopathic intracranial hypertension. J Neurol Neurosurg Psychiatry 2002;72:642–3.

20. Ball AK, Sinclair AJ, Curnow SJ et al. Elevated CSF leptin in idiopathic intracranial hypertension: evidence for hypothalamic leptin resistance? Clin Endocrinol 2008;

21. Subramanian P, Goldenberg-Cohen N, Shukla S, Cheskin L, Miller N. Plasma ghrelin levels are normal in obese patients with idiopathic intracranial hypertension (pseudotumor cerebri). Am J Ophthalmol 2004;138:109–13.

22. Lubow M, Kuhr L. Pseudotumor cerebri: comments on practical management. Neuroophthalmology 1976;IX: 199–206.

23. Tomsak RL, Niffenegger AS, Remler BF. Treatment of pseudotumor cerebri with Diamox (acetazolamide). J Clin Neuro-ophthalmol 1988;8:93–8.

24. Johnson LN, Krohel GB, Madsen RW, March GA Jr. The role of weight loss and acetazolamide in the treatment of idiopathic intracranial hypertension (pseudotumor cerebri). Ophthalmology 1998;105: 2313–7

25. Digre K. Idiopathic intracranial hypertension. Curr Treat Options Neurol 1999;1:74–81

26. Celebisoy N, G¨okc¸ay F, S¸irin H, Akyu¨rekli O. Treatment of idiopathic intracranial hypertension: topiramate vs.acetazolamide, an open-label study. Acta Neurol Scand 2007;116:322–7.

27. Dodgson SJ, Shank RP, Maryanoff BE. Topiramate as an inhibitor of carbonic anhydrase isoenzymes. Epilepsia 2000;41(Suppl 1):S35–9.

28. Corbett JJ, Thompson HS. The rational management of idiopathic intracranial hypertension. Arch Neurol 1989; 46:1049–51

29. Brourman ND, Spoor TC, Ramocki JM. Optic nerve sheath decompression for psedutomor cerebri. Arch Ophthalmol 106: 1378 -83, 1988

30. Corbett JJ, Nerad JA, Tse DT, Anderson RL. Results of optic nerve sheath fenestration for pseudotumor cerebri: The lateral orbitotomy approach. Arch Ophthalmol 106: 1391-97, 1988

31. Sergott RC, Savino PJ, Bosley TM: Modified optic nerve sheath decompression provides long-term visual improvement for pseudotumor cerebri. Arch Ophthalmol 106:1384–1390, 1988

32. Kelman SE, Heaps R, Wolf A. Optic nerve decompression surgery improves visual function in patients with pseudotumor cerebri. Neurosurgery 1992;30:391–5

33. Alsuhaibani AH, Carter KD, Nerad JA, Lee AG. Effect of Optic Nerve Sheath Fenestration on Papilledema of the Operated and the Contralateral Nonoperated Eyes in Idiopathic Intracranial Hypertension. Ophthalmology. Accepted June 23, 2010.

34. Newborg B. Pseudotumour cerebri treated by rice reduction diet. Arch Intern Med 1974;133:802–7

35. Amaral JF, Tsiaris W, Morgan T, Thompson WR. Reversal of benign intracranial hypertension by surgically induced weight loss. Arch Surg 1987;122:946–9

36. Sugerman HJ, Felton WL 3rd, Sismanis A, Kellum JM, DeMaria EJ, Sugerman EL. Gastric surgery for pseudotumor cerebri associated with severe obesity. Ann Surg 1999 May; 229(5) 634-40

37. Angiari P, Corradini L, Corsi M, Merli G. A. (1992). Pseudotumor cerebri. Lumboperitoneal shunt in long lasting cases. *Journal of Neurosurgical Science*, 36 :145–9.

38. Burgett R. A., Purvin V.A., Kawasaki A. (1997). Lumboperitoneal shunting for pseudotumor cerebri. *Neurology*, 49:734–9.

39. Eggenberger E. R., Miller N. R., Vitale S. (1996). Lumboperitoneal shunt for the treatment of pseudotumor cerebri. *Neurology*, 46:1524–30.

40. Johnston I, Besser M, Morgan M. (1988). Cerebrospinal fluid diversion in the treatment of benign intracranial hypertension. *Journal of Neurosurgery*, 69:195–202.

41. Johnston I, Paterson A, Besser M. (1988). The treatment of benign intracranial hypertension: a review of 134 cases. *Surgical Neurology,* 69:195–202.

421. Lundar T, Nornes H. (1990). Pseudotumor cerebri. Neurosurgical considerations. *Acta Neurochir,* 51:366–8.

43. Rosenberg M. L., Corbett J. J., Smith C et al. (1993). Cerebrospinal fluid diversion procedures in pseudotumor cerebri. *Neurology,* 43:1071–2.

44. Abu-Serieh B, Ghassempour K, Duprez T, Raftopoulos C. Stereotactic ventriculoperitoneal shunting for refractory idiopathic intracranial hypertension. Neurosurgery 2007;60:1043–4.

45. Woodworth GF, McGirt MJ, Elfert P, Sciubba DM, Rigamonti D. Frameless stereotactic ventricular shunt placement for idiopathic intracranial hypertension. Stereotact Funct Neurosurg 2005;83:12–6.

46. Wang V. Y., Barbaro N. M., Lawton M. T., Pitts L, Kunwar S, Parsa A. T., et al. (2007). Complications of lumboperitoneal shunts. *Neurosurgery,* 60**:**1045–1049.

47. Browd, S.R., Ragel, B.T., Gottfried, O.N., Kestle J.R.W. (2005). Failure of Cerebrospinal Fluid Shunts: Part I: Obstruction and Mechanical Failure. *J Pediatric Neurology* 34, 2: 83-92.

48. McGirt, M.J., Woodworth, G., Thomas, G., Miller, N., Williams, M., Rigamonti, D. (2004). Cerebrospinal fluid shunt placement for pseudotumor cerebri-associated intractable headache: predictors of treatment response and an analysis of long-term outcomes. *J Neurosurgery* 101: 672-632.

49. Aoki N. (1990). Lumboperitoneal shunt: clinical applications, complications, and comparison with ventriculoperitoneal shunt. *Neurosurgery,* 26**:** 998–1004

50. Abubaker K, Ali Z, Raza K, Bolger C, Rawluk D, O'Brien D. Idiopathic intracranial hypertension: lumboperitoneal shunts versus ventriculoperitoneal shunts - case series and literature review. Br J Neurosurg. 2001 Feb;25(1) 94-9.

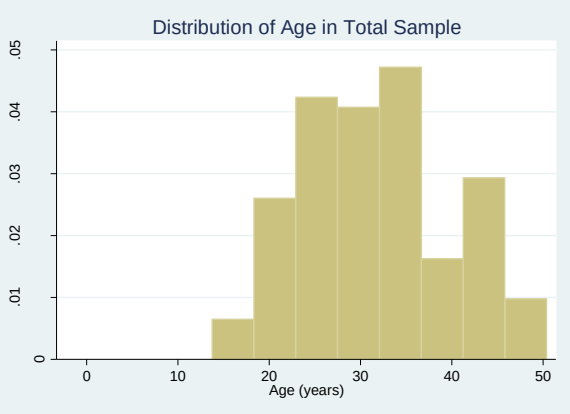
51. Vacca V. Diagnosis and Treatment of Idiopathic Normal Pressure Hydrocephalus: Ventriculoperitoneal Shunting

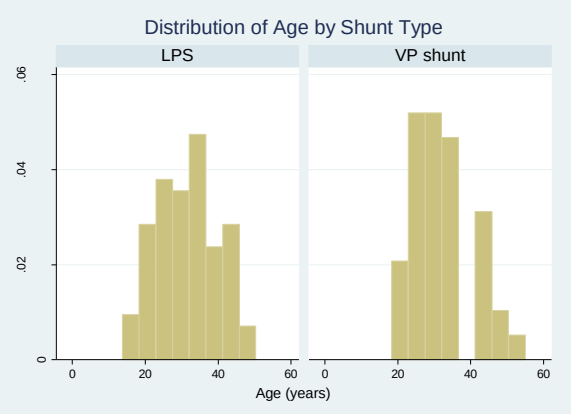
52. Friesner D, Rosenman R, Lobb BM, Tanne E. (2011). Idiopathic intracranial hypertension in the USA: the role of obesity in establishing prevalence and healthcare costs. *Obesity Review, 12*(5):e372-e380.

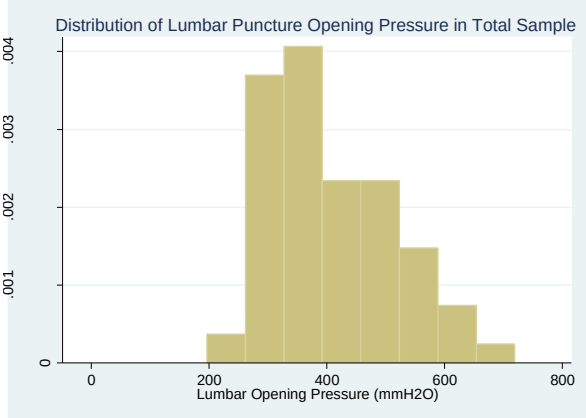
53. Curry W. T. Jr, Butler W. E., Barker F II. (2005) Rapidly rising incidence of cerebrospinal fluid shunting procedures for idiopathic intracranial hypertension in the United States, 1988–2002. *Neurosurgery*, 57:97–108.

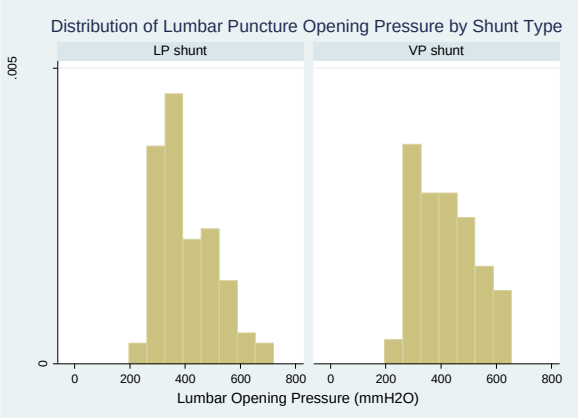
APPENDIX A

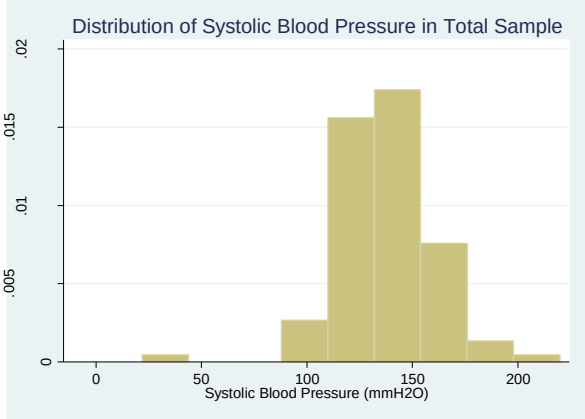
Figure A1. Histogram Distribution of Continuous Variables by Total Sample and Shunt Type

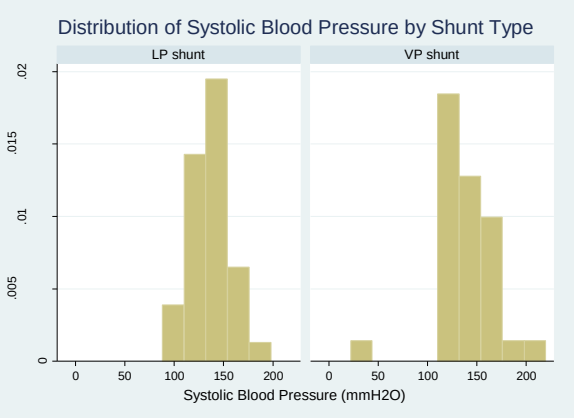


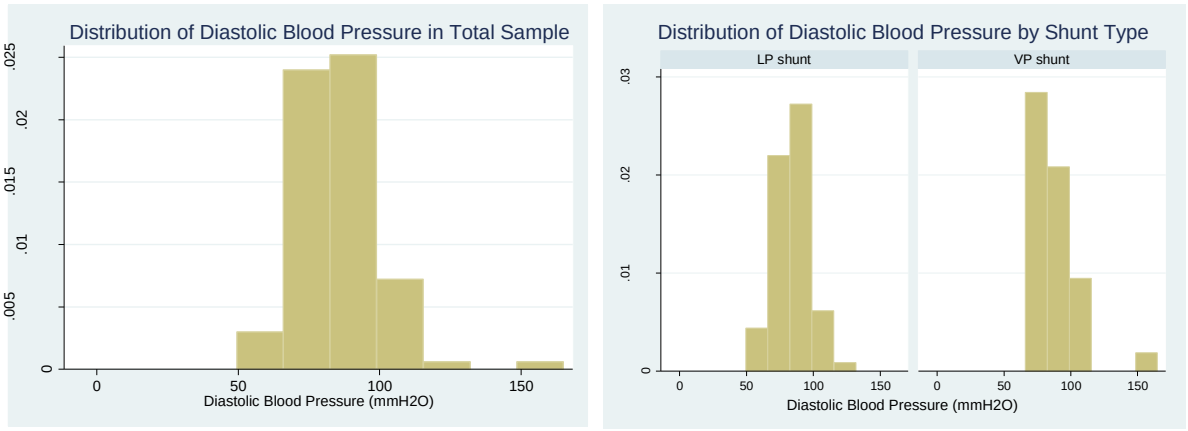








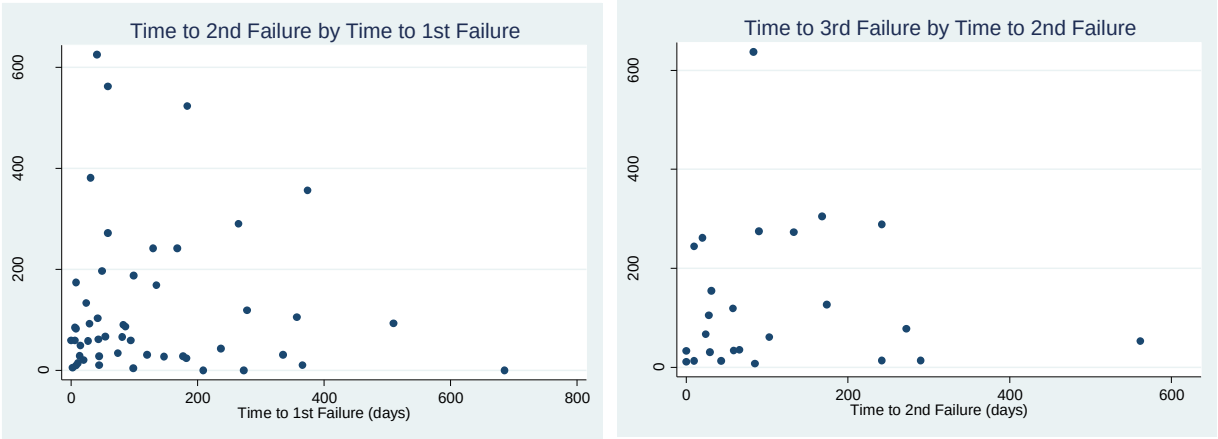




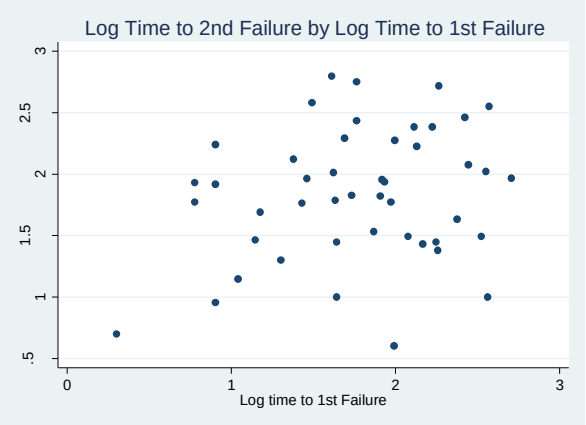
Age, systolic blood pressure, and diastolic blood pressure show approximately symmetrical distribution for total sample and by shunt type. Lumbar opening pressure shows right skew for total sample and LP group.

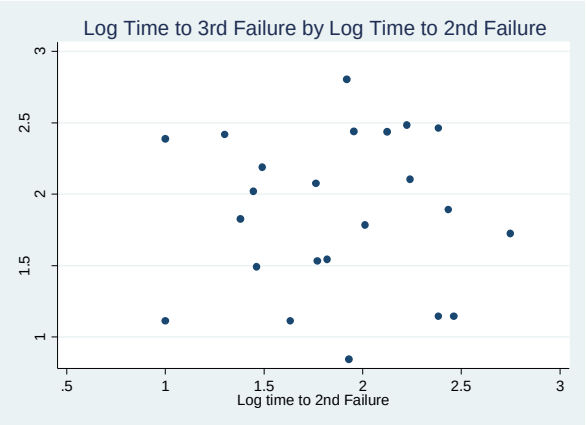
Figure A2. Scatterplot Times to Subsequent Failure based on Time to Most Recent Previous Failure.

A)



B)





A) Scatter plots show possible inverse trend between time to previous failure and time to subsequent failure. For example, longer times to first failure match up with shorter times to second failure. This relationship is most pronounced for second failure, and least pronounced for third. Plots for additional failures appeared similar (not shown). Distribution appears logarithmic rather than linear, thus need for

B) B) Scatter plots of log transformed time to failures show no relationship in distribution between time i and time i+1.

Table A3. Linear Regression Model: Log Transformed Times to Subsequent Failure Predicted by Constants and Log Time to Previous Failure

	Constant	Log Time	95% CI	p-value
Failure 1 Predict Failure 2	1.45	0.22	-0.60 – 0.49	0.122
Failure 2 Predict Failure 3	1.89	-0.10	-0.53 – 0.52	0.968
Failure 3 Predict Failure 4	1.95	-0.14	-0.85 – 0.57	0.671

After log transforming times to failure to fit previous scatterplot modeling behavior, previous failures do not predict future failures (2-4 shown here) with linear regression p>0.05. All 95% CI for previous log time to failure contained zero.

To verify our assertion that Poisson distribution did not hold due to variances larger than means, we performed univariate poisson regression on failure counts by shunt type, and then tested this model for goodness of fit (Table X). To control for mild violation of the distribution assumption that the variance equals the mean, however, we used robust standard errors from the variance co-variance matrix of estimators. Also, given that we were interested in comparing incidence rates failure, we chose to perform poisson regression with incidence rate ratios (Table 6). Goodness of fit testing suggested violation of Poisson distribution ($p < 0.05$).

Table A4. Univariate Poisson Regression: Incidence Rate Ratios for Number of Failures at Two Years by Shunt Type

	IR Ratio (95% CI)	p- value
LP shunt	-	-
VP shunt	1.32 (0.90 - 1.94)	0.160

*Goodness of fit chi2 = 232.65, pr = 0.000

At two years from first surgery, VP shunts fail 1.32 times (95%CI 0.90 – 1.94 times) for every LP shunt failure (p =0.160). Assumption of poisson distribution is violated as indicated by goodness of fit (pr =0.000 <0.05).

Violation of poisson distribution suggested that our data contained one of the following: omitted predictor variables, violated assumption of linearity, and/or over dispersion. To test for over dispersion, we performed a negative binomial regression test, and checked the likelihood ratio test that the over dispersion parameter alpha is greater than zero. Negative binomial regression suggested that over dispersion was present in our data (likelihood ratio for alpha test p<0.001). Under this model, 1.32 VP shunt failures (95%CI 0.88 – 1.98 failures) are estimated for every LP shunt failure (p= 0.181) (see results).

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CERTIFICATE OF APPROVAL

This is to certify that the Master's thesis of

Richard Lewis Martin III

has been approved

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