Endovascular Thrombolysis or Thrombectomy for Cerebral Venous Thrombosis: Study of Nationwide Inpatient Sample 2004-2014

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Background and purpose: 15% of cerebral venous thrombosis (CVT) patients have poor outcomes despite anticoagulation. Uncontrolled studies suggest that endovascular approaches may benefit such patients. In this study, we analyze Nationwide Inpatient Sample (NIS) data to evaluate the safety and efficacy of endovascular therapy (ET) versus medical management in CVT. We also examined the yearly trends of ET utilization in the United States. *Methods:* International Classification of Diseases, Ninth Revision, Clinical Modification codes were utilized to identify CVT patients who received ET. To make the data nationally representative, weights were applied per NIS recommendations. Since ET was not randomly assigned to patients and was likely to be influenced by disease severity, propensity score weighting methods were utilized to correct for this treatment selection bias. Outcome variables included in-hospital mortality and discharge disposition. To determine if our primary outcomes were associated with ET, we used weighted multivariable logistic regression analyses. *Results:* Of the 49,952 estimated CVT cases, 48,704 (97%) received medical management and 1248 (3%) received ET (mechanical thrombectomy [MT] alone, N = 269 [21%], MT ± thrombolysis, N = 297 [24%], and thrombolysis alone, N = 682 [55%]). Patients who received ET were older with more CVT associated complications including venous infarct, intracranial hemorrhage, coma, seizure, and cerebral edema. There was a significant yearly rise in the use of ET, with a trend favoring MT versus thrombolysis alone. ET was independently associated with an increased risk of death (odds ratio 1.96, 95% confidence interval 1.15-3.32). *Conclusions:* Patients receiving ET experienced higher mortality after adjusting for age and CVT associated complications. Large, well designed prospective randomized trials are warranted for further evaluation of the safety and efficacy of ETs.

Key Words: Cerebral venous thrombosis—thrombolysis—thrombectomy—outcome—trends

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Introduction

Anticoagulation is the first-line treatment for cerebral venous thrombosis (CVT).[1-4] However, some question its efficacy because a subset of patients does not respond, and their condition continues to deteriorate.[5-7] Data from case reports and uncontrolled case series suggest that endovascular approaches may benefit patients with risk factors for a poor predicted prognosis such as male sex, age more than 37 years, coma, mental status disorder, and intracranial hemorrhage (ICH).[8,9] Endovascular techniques have the potential to rapidly recanalize an occluded venous sinus allowing for prompt restoration of blood flow, decreased intracranial pressure, and reduction of related symptoms.[10] Additionally, direct delivery of thrombolytic therapy reduces the risk of systemic side effects.[11] On the other hand, endovascular intervention may increase the risk of vessel dissection, ICH, and pulmonary embolism.[12]

Systematic reviews have reported good outcomes after endovascular treatment (ET), but these studies are prone to publication bias and under-reporting of poor-outcomes.[9,13,14] Preliminary results of Thrombolysis or Anticoagulation for Cerebral Venous Thrombosis (TO-ACT) trial were recently presented at the European Stroke Organization Conference. TO-ACT is a randomized open-label trial that compared 12-month modified Rankin scores (mRS) in patients who received medical management and endovascular thrombolysis with or without mechanical clot removal to those who received medical management (therapeutic doses of heparin) alone. The trial allowed treating physicians to decide about enrollment in the endovascular arm if uncertain about optimal treatment.[15] Despite optimistic expectations, the initial results of this trial did not show a trend toward favorable outcomes in patients who received ET. Reproducibility of these results in clinical practice, given the potential selection bias introduced by the trial's eligibility criteria, remains to be established.

Use of a large, multicenter national patient database may help to reduce sampling error and increase generalizability.[16] The Nationwide Inpatient Sample (NIS) is the largest all-payer inpatient health care database in the United States representing a 20% stratified sample of community hospitals and approximately 7 million annual hospital admissions.[16] NIS is considered to provide an accurate estimate of national outcomes.[16] In this study, we analyze data from the NIS to evaluate the safety and efficacy of ET compared to medical management in CVT. We also evaluate the trends of various ETs utilized during the period of study.

Materials and Methods

Study Population

We analyzed data extracted from the NIS for the years 2004-2014. We obtained an Institutional Review Board exemption for waivers of informed consent and Health Insurance Portability and Accountability Act authorization. CVT patients were identified utilizing International Classification of Diseases, Ninth Revision, and Clinical Modification (ICD 9-CM) codes: 437.6 for nonpyogenic thrombosis of intracranial venous sinus, 325 for phlebitis and thrombophlebitis of intracranial venous sinuses and 671.5 for cerebral venous sinus thrombosis nonpyogenic in pregnancy. The following baseline variables were collected: age, sex, race, length of stay, death, and discharge disposition. Data related to mechanical thrombectomy (MT) ± thrombolysis were searched using ICD 9-CM codes 39.74 for endovascular removal of obstruction from head and neck vessel(s) and 99.10 for any injection or infusion of thrombolytic agent. To identify the predisposing conditions associated with CVT, we used the Clinical Classification Software for the followings groups: hematologic conditions, central nervous system infections, systemic inflammatory diseases, any malignant cancer, benign brain tumors, and traumatic brain injury. We identified common CVT associated complications including ICH, venous infarct, seizures, cerebral edema or midline shift, and coma utilizing ICD 9-CM codes. Please see supplementary Table 1 for a complete list of ICD 9-CM and Clinical Classification Software codes. Severe CVT was defined as any patient with at least one of the following complications: ICH, seizures, need for endotracheal intubation, cerebral edema or midline shift, and coma.

Data Validation

We conducted an internal validation of the accuracy of ICD 9-CM codes by performing a query on a previously collected CVT database.

Outcome Measures

Our primary outcome measures were inpatient death and discharge disposition. NIS documents discharge as routine (home), short-term hospital, home health and other (skilled nursing facility, intermediate care facility, another type of facility, and leave against medical advice). Full details are available at www.hcup-us.ahrq.gov/db/vars/disp/nisnote.jsp.

Statistical Analysis

Sample weights were applied to each admission per recommendations from the NIS.[17] In NIS, each record has its own unique weight relative to the discharge population to allow users to make inferences regarding the overall population. By applying weights, the sample and any inferences drawn from it, are representative of the population; the goal being reduction of bias in inferences.[18] Detailed information on the design of the NIS is available at www.hcup-us.ahrq.gov.

Table 1. *Baseline characteristics and standardized differences between treatment groups in the study population using survey weights both before and after balancing for treatment propensity score weights*

	Survey weighted			Survey and propensity score weighted		
	Endovascular therapy			Endovascular therapy		
	Yes	No		Yes	No	
Characteristics	**N** = 1248	**N** = 48,704	**d***	**N** = 47,095	**N** = 49,947	**d***
Demographics						
Age, mean (SE)	39.2 (1.11)	36.8 (.21)	.12	36.43 (1.39)	36.87 (.21)	−.02
Gender, female (%)	852 (68.25)	32,187 (66.16)	.04	31,329 (66.52)	32,983 (66.08)	.009
Race						
White (%)	707 (68.43)	25,465 (62.38)	.14	26,616 (68.99)	26,122 (62.36)	.15
Black (%)	165 (15.94)	6623 (16.22)	−.008	6097 (15.80)	6802 (16.24)	−.01
Hispanic (%)	97 (9.43)	5297 (12.98)	−.12	4534 (11.75)	5428 (12.96)	−.04
Other (%)	64 (6.21)	3436 (8.42)	−.09	1331 (3.45)	3538 (8.45)	−.21
Disease severity						
Coma (%)	65 (5.22)	442(.91)	.25	779 (1.66)	519 (1.04)	.04
Venous infarction (%)	268 (21.51)	3,199 (6.57)	.44	4074 (8.65)	3482 (6.97)	.05
Intracerebral hemorrhage (%)	473 (37.89)	4,663 (9.57)	.70	5454 (11.58)	5153 (10.32)	.03
Seizure (%)	447 (35.78)	7967 (16.36)	.45	9558 (20.30)	8426 (16.87)	.08
Cerebral edema/midline shift (%)	363 (29.09)	3313 (6.80)	.61	4130 (8.77)	3690 (7.39)	.04
Respiratory failure needing endotracheal intubation (%)	294 (23.57)	3752 (7.70)	.45	4907 (10.42)	4062 (8.13)	.06
Predisposing conditions						
Infection (%)	158 (12.70)	4526 (9.29)	.11	4789 (10.17)	4680 (9.37)	.03
Cancer (%)	125 (10.01)	5699 (11.70)	−.05	4495 (9.54)	5870 (11.75)	−.07
Hematological disorders (%)	485 (38.83)	8441 (17.33)	.49	17,172 (36.46)	8737 (17.49)	.43
Traumatic head Injury (%)	35 (2.78)	2784 (5.72)	−.15	1868 (3.97)	2867 (5.74)	−.09
Severe dehydration (%)	73 (5.87)	2227 (4.57)	.06	1907 (4.05)	2286 (4.58)	−.02
Disposition						
Routine (home) (%)	574 (46.02)	32,759 (67.28)	−.44	28,402 (60.31)	33,401 (66.87)	−.14
Short term hospital (%)	69 (5.52)	2772 (5.69)	−.007	2120 (4.24)	2849 (6.05)	−.05
Home health (%)	117 (9.36)	5631 (11.56)	−.07	6076 (12.17)	5761 (12.23)	.04
Other (%)	290 (23.25)	5905 (12.31)	.30	7223 (15.34)	6186 (12.38)	.08
Died (%)	198 (15.86)	1628 (3.34)	.43	3273 (6.55)	1740 (3.70)	.12

*Standardized difference, or the difference in means or proportions in each treatment group divided by the standard error of the difference. Values above 0.2 indicate imbalance.

However, use of ET was not randomly assigned to patients and was likely to be influenced by disease severity, which has the potential to confound associations with our primary outcome. To correct for this treatment selection bias, we used propensity score weighting methods, as described by Ridgeway et al.[19] Here, a survey weighted logistic regression was used to calculate the probability that each admission received ET (p_x) based on age and disease severity factors (ie, coma, venous infarct, ICH, seizures, cerebral edema/midline shift, and respiratory failure). The propensity score weights were then defined as $1/p_x$ for those that received ET and $1/(1-p_x)$ for those that did not. The final weights that were applied to admissions and used in subsequent analyses were calculated by multiplying the sample weights by the propensity score weights. After these final weights were applied, all variables (ie, demographics, disease severity, predisposing conditions, and disposition) were assessed for improvement in balance between treatments. For this, we used standardized differences (ie, the difference in means or proportions divided by the standard error of the difference). Variables with standardized differences that had an absolute value above 0.2 were considered unbalanced.

To determine if our primary outcomes were associated with ET, we used weighted multivariable logistic regression analyses, where the weights for admission were the final weights described above. Variables included in this model were whether or not ET was performed and any conditions that may predispose an outcome (ie, systemic infection, cancer, hematological disorders, traumatic head injuries, and severe dehydration).

Trends of ET utilization were assessed using a Cochran−Armitage test of trends.

For all analyses, statistical significance was set at $P \leq .05$. Propensity score and logistic regression analyses were performed using the "survey" package[20] in R statistical software,[21] and trend analyses were performed using SAS statistical software, version 9.3.

Table 2. *Propensity score analysis relating age and disease severity measures to the likelihood of endovascular therapy (ET)*

Variable	Odds Ratio	Lower CI	Upper CI	*P* Value
Age, years	.10	.10	1.00	.66
Coma	1.81	1.34	2.42	<.001
Venous infarction	2.41	2.07	2.79	<.001
Intracerebral hemorrhage	3.35	2.93	3.82	<.001
Seizure	1.65	1.45	1.87	<.001
Cerebral edema/midline shift	2.50	2.16	2.89	<.001
Respiratory failure needing endotracheal intubation	1.77	1.52	2.05	<.001

Results

Source Validation

The accuracy of primary diagnostic ICD 9 codes for CVT was internally validated. Out of 191 patients at the University of Iowa Hospitals and Clinics who were coded for CVT diagnosis, 15(8%) were not CVT cases.

Demographics and Baseline Characteristics

In our study, we had a total of 10,092 cases of CVT (unweighted count). When the weights were applied to generate a national estimate, the total number of CVT cases was 49,952. 9.839 (97%) cases (weighted N = 48,704) received only medical management and 253 (3%) patients (weighted N = 1,248) received ET. 2022 (weighted N = 10,016) (20%) were severe CVT (as defined in the methodology section). Out of the 253 cases that received ET, 59% (N = 147, weighted N = 726) were clinically severe cases. On the other hand, 93% of clinically severe CVT cases did not receive ET.

Baseline characteristics and outcomes of our CVT population are summarized in Table 1. Patients who underwent ET had more CVT associated complications including venous infarct, ICH, coma, seizures, and cerebral edema with midline shift (Table 1). These patients also had higher likelihoods of respiratory failure requiring endotracheal intubation (Table 1). Among suspected etiologies of venous thrombosis, patients who received ETs had higher chances of having hematological disorders (38% versus 17%, $P < .0001$). The data on the timing of procedure from the day of admission were available for 174 out of 253 endovascular patients. The median number of days from admission to procedure was 1 (IQR 0-3).

When admissions were weighted by their propensity score weights in addition to the survey weights, those who received and did not receive ET showed considerably higher balance in baseline characteristics, approximating quasi-random assignment to treatment. In particular, under this weighting scheme, confounding factors relating to age and disease severity (ie, coma, venous infarct, ICH, seizures, cerebral edema/midline shift, and respiratory failure) were now similar across treatment groups (Table 1). However, the proportion of admissions that were a race other than white, black, or Hispanic and who had hematological disorders were still not balanced after propensity score weighting (Table 1).

Propensity Score Analysis

The propensity score model indicated significant associations between disease severity measures and the likelihood of receiving ET (Table 2). Coma, venous infarct, ICH, seizures, cerebral edema/midline shift, and respiratory failure were all associated with a higher likelihood of receiving ET (Table 2). There was no significant association between age and ET (Table 2). Overall, the propensity score model did well at predicting ET (area under the receiver-operator curve [AUC] = .75).

Mortality and Poor Discharge Outcomes

After applying an inverse probability of treatment weight as determined by the propensity scores (Table 3),

Table 3. *Survey and propensity score weighted logistic regression results for in-hospital mortality for All cerebral venous thrombosis (CVT) patients*

Variable	Odds Ratio	Lower CI	Upper CI	*P* value
Endovascular treatment*	1.97	1.16	3.34	.01
Infection	.82	.35	1.95	.66
Cancer	1.29	.69	2.44	.43
Hematological disorders	1.31	.62	2.76	.48
Traumatic head injury	.98	.45	2.14	.95
Severe dehydration	.24	.11	.55	.001

*All observations are weighted according to the product of the survey weight and the inverse probability of endovascular treatment as determined by a propensity score analysis that included age and CVT severity measures (Table 2).

Table 4. *Survey and propensity score weighted logistic regression results for routine discharge (home) for all cerebral venous thrombosis (CVT) patients*

Variable	Odds Ratio	Lower CI	Upper CI	*P* value
Endovascular treatment*	.78	.57	1.09	.14
Infection	.61	.37	.99	.05
Cancer	.60	.37	.99	.05
Hematological disorders	.77	.49	1.09	.13
Traumatic head injury	.86	.44	1.66	.64
Severe dehydration	.54	.29	1.02	.06

*All observations are weighted according to the product of the survey weight and the inverse probability of endovascular treatment as determined by a propensity score analysis that included age and CVT severity measures (Table 2).

we found ET and severe dehydration were significantly associated with mortality (Table 3). ET was associated with an increased risk of death (Odds Ratio [OR] = 1.965, 95% confidence interval [1.16, 3.34]). Severe dehydration was associated with a decreased risk of death (OR = 0.24 [0.11, 0.55]). This model fits significantly better overall than an intercept-only model (survey and propensity score adjusted likelihood ratio test, $P = .050$).

However, after propensity score weighting, ET was not significantly associated with the likelihood of a routine (home) discharge (Table 4). Here, systemic infection (OR = 0.61 [0.37, 0.99]) and cancer (OR = 0.60 [0.37, 0.99]) were associated with a significantly lower probability of routine discharge (Table 4). Again, this model fits significantly better overall than an intercept-only model (survey and propensity score adjusted likelihood ratio test, $P = .01$).

We note that multivariate regression models of mortality and routine discharge that included disease severity measures to adjust for residual confounding after applying the inverse probability of treatment weights yielded qualitatively similar results on the relationship between our outcomes and endovascular treatment (results not shown).

ET Subgroup Analyses

We also analyzed patients who received either MT ± thrombolysis versus thrombolysis alone using survey weights only. There were 682 cases of thrombolysis alone, 297 cases of both MT ± thrombolysis and 269 cases of MT alone (Table 5).

Patients who received thrombolysis alone had lesser chances of having venous infarct, ICH, coma or midline shift. MT alone was performed predominantly in those patients who had ICH (Table 5).

Trends of ET Utilization

Overall, there were an increasing number of endovascular procedures done to treat CVT over the years. In the first 6 years, there were 468 estimated number of CVT cases treated endovascularly versus 780 in the last 5 years. There was a significantly increasing trend of utilization of the MT ± thrombolysis over thrombolysis alone over the years (Fig 1).

Discussion

Our study reports several interesting findings that merit thoughtful consideration of the current endovascular practice regarding the treatment of CVT, especially severe CVT. Patients who were older, had higher comorbidity, and hematological disorders were more likely to receive ET. Thus, worse outcomes were expected and not necessarily the result of ET. The use of propensity score weighting alleviated some of this potential treatment selection bias, and after adjusting for this bias, ET was associated with significantly higher mortality. ET was not, however, independently associated with poor discharge outcomes. These results are consistent with the recently concluded TO-ACT trial which failed to show a benefit in 12-month mRS in patients who were managed with ET + medical management versus medical treatment alone. TO-ACT trial enrolled 31 patients in the ET arm and 32 patients in the standard treatment arm. Sixty five percent patients in the ET arm achieved mRS of 0-1 versus 66% patients in the standard treatment arm (OR 0.95, 95% confidence interval 0.34-2.68).

Our study also showed a steady increase in the use of MT ± thrombolysis over thrombolysis alone as the procedure of choice for treatment of this rare disease. When subgroup analyses were performed on ET patients, comparing those that received MT (whether with or without thrombolysis) to those that only received thrombolysis, there was no significant in mortality or routine discharge between these ET options. This result holds even if we restrict the comparison to MT only and thrombolysis only.

Overall, 15% mortality in the study population who received ET is slightly higher than 9.9%, 12%, and 14.3% reported in the recently published case series.[9,22,23] The lower mortality rates in these studies may be due to publication bias of under-reporting poor outcomes. Our study also involves a high percentage (55%) of patients who received thrombolysis alone which may offset the unique beneficial effects of MT found in prior reviews.[9,22,23]

Table 5. *Baseline characteristics of the endovascular population (weighted)*

	Endovascular therapy treatments		
	Mechanical thrombectomy (MT) N = 269	MT & Thrombolysis N = 297	Thrombolysis N = 682
Demographics			
Age (mean ± SD)	40.60 ± 38.99	39.89 ± 37.53	38 ± 39.97
Gender, female (%)	203 (75.35)	194 (65.34)	455 (66.73)
Race %			
White	159 (66.49)	173 (71.21)	375 (68.05)
Black	34 (14.37)	40 (16.63)	90 (16.31)
Hispanic	35 (14.76)	*	52 (9.47)
Other	*	20 (8.11)	34 (6.17)
Disease severity			
Coma (%)	20 (7.47)	30 (10.11)	15 (2.16)
Venous infarction (%)	80 (29.59)	73 (24.68)	116 (16.95)
Intracerebral hemorrhage (%)	147 (54.64)	139 (46.69)	187 (27.44)
Cerebral edema/midline shift (%)	130 (48.37)	140 (47.03)	93 (13.65)
Respiratory failure needing endotracheal intubation (%)	72 (26.72)	79 (26.67)	143 (20.98)
Predisposing conditions			
Infection (%)	35 (12.94)	45 (15.19)	78 (11.51)
Cancer (%)	31 (11.52)	30 (10.21)	64 (9.33)
Hematological disorders (%)	105 (38.94)	149 (49.93)	231 (33.93)
Traumatic head injury (%)	*	15 (4.93)	20 (2.95)
Severe dehydration	*	30 (10.03)	33 (4.90)
Disposition			
Routine (home) (%)	102 (37.91)	124 (41.68)	349 (51.44)
Short term hospital (%)	20 (7.29)	15 (4.99)	34 (5.08)
Home Health (%)	83 (30.82)	78 (26.36)	125 (18.39)
Other (%)	*	20 (6.87)	86 (12.69)
Died (%)	54 (20.12)	60 (20.11)	84 (12.40)

*Values suppressed due to N ≤10.

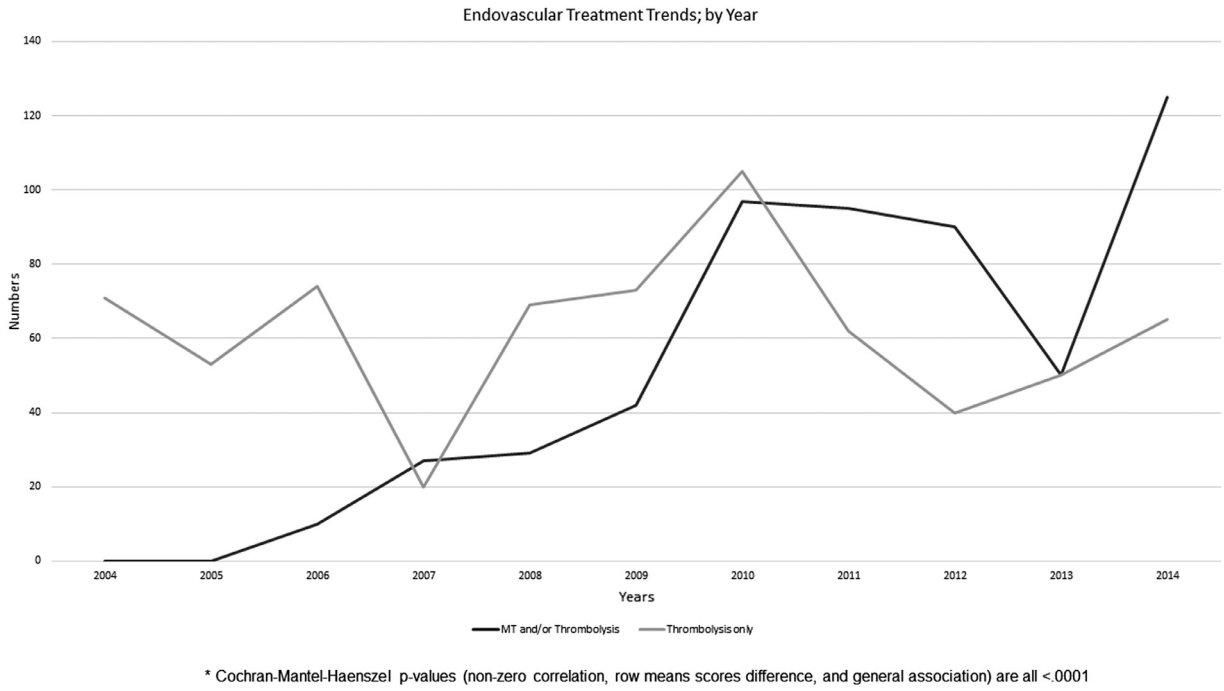

Figure 1. *Endovascular treatment trends; by year.*

Forty one percent of patients who received ET were not clinically severe cases of CVT, whereas 93% of clinically severe cases of CVT were not treated with ET. This discrepancy may be a result of inadequate standardized guidelines and rationale for utilizing endovascular procedures. Current guidelines do not recommend ET as a first-line treatment for CVT.[3,24]

One surprising result from our study is an inverse relationship between dehydration and mortality. Dehydration is a known risk factor for CVT.[25] However, there is a lack of data on its effect on CVT prognosis when compared to other risk factors. Compared to genetic and other secondary clotting disorders, dehydration is readily reversible with simple hydration. In fact, kawahara et al reported a case of rapid recanalization of CVT secondary to severe dehydration after treatment with fluids.[26] However, Liu K et al reported an overall poor prognosis in their series of 220 CVT patients. Eighty five of those were dehydrated.[27] Overall, several factors could lead to this association, including underreporting or not accounting for a variable in the multivariate analysis that could be driving this relationship.

Our study does not demerit the hope and promise associated with ET in devastating cases of CVT. However, as with any neuroendovascular technique, proper and timely patient selection may be the key for identifying appropriate ET candidates. Poor prognosis in CVT is directly correlated with involvement of cerebral cortical veins which may lead to ICH, venous infarction, and/or edema (traditional poor prognostic factors in CVT). Current techniques, though refined, are still limited in safely accessing the culprit small cortical veins.

Overall, our study is the largest series of patients who received ET for CVT. However, this study is limited by the possible coding errors and the lack of clinical and radiological information in the NIS dataset. Our own internal validation suggested 8% coding errors. This is a single institutional validation and the coding errors percentage could be much higher throughout the study sample. As the study is observational, it carries an inherent indication bias (patients with worse clinical condition on admission were treated more aggressively, and had a poorer outcome, irrespective of whatever treatment they received), although our use of propensity score weighting helps to adjust for some of this bias. In addition, many cases of severe CVT may have been missed if CVT involved deep venous system as these patients may not have midline shift or ICH on presentation. Due to inherent limitations with the NIS database, we were unable to determine whether the listed CVT complications happened before or after the procedures. In addition, the ICD 9 code for tissue plasminogen activator infusion involves any infusion whether arterial or venous. However, use of intravenous tissue plasminogen activator in the setting of CVT, although previously reported, has been extremely rare and may not have changed the overall outcome.[28] Outcomes were measured at discharge which is not a fixed time variable and dependent on the total length of stay. We were not able to include patients beyond year 2014 because of overlap between ICD 9 and ICD 10 codes and difficulties in extracting reliable data.

Conclusions

Because ET was associated with higher mortality after adjusting for age and CVT associated complications, our results suggest caution in using ET in patients with CVT. However, our analytical techniques do not overcome the issue of several unmeasured confounders described in the limitation section. Current guidelines do not recommend ET as a first-line treatment for CVT and the findings of this study do not predict any major modifications in that statement soon. Large, well designed prospective randomized trials are warranted for further evaluation of the safety and efficacy of ETs. However, those might need to be preceded by the development of better stratification tools for early identification of high risk CVT patients that are unlikely to respond to standard anticoagulation therapy. In the meanwhile, ET should continue to be a consideration for patients having progressive neurological deterioration despite optimized medical therapy.

Disclosures

There is no institutional conflict of interest regarding this article. The author conflicts of interest are as follows: Dr Elias, Consultant/Speaker Bureau for Penumbra, Inc. The other authors report no conflicts.

Supplementary Materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jstrokecerebrovasdis.2019.03.025.

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