Endovascular Treatment for Cerebral Venous Sinus Thrombosis: Comparison among Different Endovascular Procedures

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Abstract

Background: Cerebral venous sinus thrombosis (CVST) is a rare, treatable cause of stroke. Even though CVST has an established medical treatment, 15% of patients remain refractory to treatment. These patients may be candidates for endovascular treatment (EVT), yet the selection of patients remains a challenge. The study aims to understand the profile and outcome of patients treated with EVT and the type of procedure associated with good outcomes. **Methods:** This is a single-center, retrospective analysis of CVST patients who underwent EVT from 2009 till 2022. Patients who received only medical management were excluded. Modified Rankin Scale (mRS) ≤2 at 3 months was taken as the primary outcome. Secondary outcomes assessed were hospital stay, death, recurrence, mRS ≤ 2 at discharge, and angiographic recanalization. **Results:** Fifty-two patients were included. Twenty-eight (53.8%) were males; the mean age was 33.3 ± 12.3 years. Headache (*n* = 44, 84.6%) predominated among the symptoms. The common risk factors were anemia (*n* = 13, 25.5%) and hyperhomocysteinemia (*n* = 13, 25.5%). Worsening of sensorium (*n* = 21, 40.3%) and non-improvement of symptoms (*n* = 15, 28.8%) were the common indications for the procedure. Twenty-five (48.1%) people underwent *in situ* thrombolysis (IST). Death occurred in eight (15.3%) patients. Thirty-six (73.5%; 36/49) patients had a good outcome at 3 months. IST had a significantly better outcome (mRS ≤ 2, *n* = 20, 80%) compared to other procedures (*P* = 0.04). Hospital stay was lesser in the IST subgroup, but without statistical significance. Midline shift >5 mm (odds ratio [OR] 6.8 [1.5–30.9], *P* = 0.01) and Glasgow Coma Scale <9 before the procedure (OR 27.2 [3.1–236.4], *P* = 0.002) predicted bad outcomes at 3 months. Female gender (OR 4.5 [1.07–8.8], *P* = 0.03), presence of altered sensorium (OR 10.2 [1.2–87.5], *P* = 0.01), encephalopathic syndrome (*P* = 0.02), presence of parenchymal bleed (OR 3.7 [0.9–4.5], *P* = 0.04), and midline shift (OR 4.8 [1.1–20.2], *P* = 0.03) were associated with poor outcome at discharge. **Conclusion:** EVT yielded good outcomes in carefully selected, medically refractory patients of CVST. IST performed well compared to other procedures.

Keywords: Endovascular treatment, *in situ* thrombolysis, mechanical thrombectomy, refractory cerebral venous sinus thrombosis

Introduction

Young strokes can be caused by cerebral venous sinus thrombosis (CVST). The International Cerebral Vein Thrombosis Study reports that even with the best medical care, 13% of patients may still experience adverse outcomes.[1] Given the condition's rarity, there should be high clinical suspicion, despite the variability in CVST presentation.[2] Although there are a lot of case reports and retrospective studies about the effectiveness of endovascular therapy (EVT) in CVST, there needs to be more high-quality research to support this claim. EVT in CVST may be advantageous for a subset of patients. Currently, there are no established protocols for neuro interventions in CVST.[3] EVT can be administered as mechanical thrombectomy (MT), *in situ* thrombolysis (IST), or a combination of these procedures. IST involves administering thrombolytics close to or inside the thrombus.[4] There are different ways to do MT, such as using aspiration catheters to remove the clot, stent retrievers to get the clot back, or Fogarty catheters with balloon angioplasty for Fogarty balloon thrombectomy. It is also possible to use a specialized Angiojet™ device, which breaks up and aspirates the clot using its hydrodynamic thrombolytic properties. More information is needed to indicate which of these is effective. In this study, we aim to highlight the factors influencing the outcomes of patients receiving EVT for CVST, compare and determine which procedure performs better, and share our experience of treating patients with various techniques.

Methodology

This is a single-center, retrospective study of CVST patients who underwent EVT from 2009 to 2022. The diagnosis of CVST was confirmed by magnetic resonance imaging and magnetic resonance venography or computed

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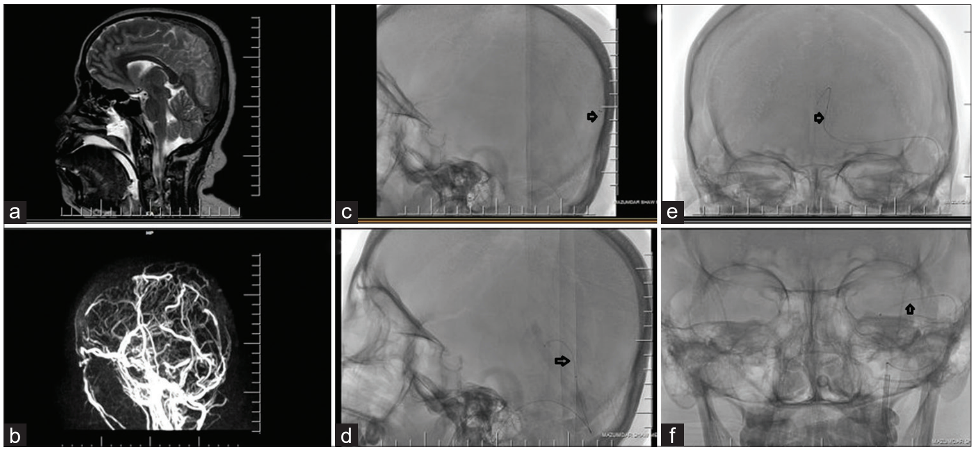

Figure 1: (a and b) Representational images- MRI T2 sagittal and MRV show extensive thrombus in the superior sagittal sinus, deep sinuses, and bilateral transverse sinus. (c) X-ray skull lateral projection shows aspiration catheter in the superior sagittal sinus. (d) Microcatheter in the straight sinus for *in situ* thrombolysis. (e) Microcatheter in the superior sagittal sinus for *in situ* thrombolysis. (f) Long sheath in IJV and microcatheter in the left transverse sinus for *in situ* thrombolysis. MRI = magnetic resonance imaging, MRV = magnetic resonance venography, IJV = Internal jugular vein

tomography venography based on the availability and patients' hemodynamic status.

We included patients with cerebral sinus thrombosis who underwent EVT. The indications of EVT were patients aged above 18 years, patients developing new deficits (worsening of power, double vision, vision loss) on maximal medical therapy, patients with worsening of sensorium status epileptics on maximal medical treatment, and patients whose condition failed to improve even after 2 days of medical therapy (refractory CVST patients). We excluded patients who improved with medical management alone, pregnant women, and children. The International Classification of Disease code was used to search the files, the respective patients were included, and relevant data was collected. Images of the patients were accessed using the picture archiving and communication system. The thrombus was considered acute when the T1 images were isointense and the T2 images were hypointense, subacute when both were hyperintense, and chronic when both were hypointense.

The study aims to understand the profile and outcome of patients treated with EVT and the type of procedure associated with good outcomes.

The choice of procedure was left to the operator. In our institution, we perform mechanical thromboaspiration, IST, or a combination of these procedures. While doing the procedure, if the Terumo guidewire passed through the clot, the aspiration catheter was advanced and thromboaspiration was done. After thromboaspiration, check shoot was done. If the sinus had recanalized, the procedure was stopped. If not, IST was started. If the Terumo guide wire did not pass in the first hand, IST was preferred. Other factors like thrombus load (if more, the *in situ* procedure was preferred), size of parenchymal bleed, number of sinuses involved (if more than one was involved, the *in situ* procedure was preferred), etc., also played a role in selection of the procedure.

IST was performed by introducing a guide catheter (Envoy; Codman and Shurtleff, Inc, Rayham, MA, USA) via the femoral vein into the internal jugular vein. Then, a microcatheter (SL10, Echelon) was negotiated into a frontal position in the superior sagittal sinus. Then, 1 lakh units/h of urokinase or 1 mg/h of recombinant tissue plasminogen activator (rTPA) was used till antegrade flow in the sinus was achieved or the patient developed any side effects of the infusion. Digital subtraction angiogram was repeated daily to check for recanalization, and the tip of the microcatheter was repositioned in such a way that the tip lay inside the thrombus. Intravenous heparin with a full dose was continued during thrombolytic therapy with urokinase; however, when rTPA was used, we halved the dose of heparin [Figure 1].

Aspiration thrombectomy (mechanical thromboaspiration) was done by advancing a long sheath into the internal jugular vein and coaxially introducing an aspiration catheter (ACE68, Jet7, etc.). The Terumo wire was initially passed into the sinus, and the clot was macerated. The clot was then aspirated using a Penumbra aspiration pump. Sinus recanalization was examined by injection of contrast through the artery or vein.

When the thrombus burden of CVST was very high, mechanical thromboaspiration was initially done, and after removing the aspiration catheter, a microcatheter was introduced and inset thrombolysis was started.

The sinus was said to be partially recanalized when the residual stenosis was >50%, but antegrade flow was present. The term near complete was used when residual stenosis was <50%, and complete recanalization was said to be present when there was no residual stenosis.[5]

The primary outcome at follow-up visits was assessed retrospectively by telephone interview by the primary investigator. Modified Rankin Scale (mRS) (0 = complete recovery, 6 = death) was used to express the outcome. mRS ≤ 2 was taken as a good outcome. Secondary outcomes assessed were duration of hospital stay, death, recurrence, mRS ≤ 2 at discharge, and angiographic recanalization.

Statistical analysis

Data were analyzed using IBM Statistical Package for the Social Sciences software for Windows version 21. Baseline patient characteristics were expressed using mean and standard deviation or median with range for continuous variables and frequency with percentage for categorical variables. To compare the outcomes among the three interventional procedures, the Kruskal–Walli's test was used in the case of continuous variables and the Chi-square/Fischer's exact test in the case of categorical variables. Comparison of variables between good outcome and poor outcome was done using Mann–Whitney U test and Chi-square test/Fischer's exact test, depending on the type of data. Factors associated with poor outcomes at 3 months were analyzed using univariate regression analysis. *P* value < 0.05 was considered statistically significant.

Results

Fifty-two patients satisfied the inclusion and exclusion criteria. The primary outcome and mRS at discharge were available for 49/52 patients. Table 1 shows the demographic data of the patients enrolled in the study. Twenty-eight (53.8%) patients were males, and the mean age of patients was 33.3 (standard deviation: 12.3) years. Headache (84.6%) predominated among the symptoms, and raised intracranial tension (34.6%) was the most common syndrome in our cohort. The common risk factors were anemia (25%) and hyperhomocysteinemia (25%). Worsening of sensorium (40%) and non-improvement of symptoms (28.8%) were the common indications for the procedure. Twenty-five (48.1%) people underwent IST. Among the patients admitted, parenchymal hemorrhage, midline shift, and mass effect were present in 34 (65.3%), 21 (40.8%), and 33 (63.4%) patients, respectively. The superior sagittal sinus was the most commonly involved sinus (88.2%) in our study. We used novel anticoagulants in 22% of patients in the cohort. Death occurred in eight (15.3%) patients. We had only two patients who had a recurrence in our cohort.

Among the patients who underwent EVT, 36 (73.5%) had a good outcome at 3 months. Table 2 shows a comparison of the variables among the three procedures. The IST subgroup had a significantly better outcome than mechanical thromboaspiration and a combination of procedures [Figure 2]. Furthermore, angiographic recanalization was also better in patients who underwent IST compared to other methods. The mean Glasgow Coma Scale (GCS) before the procedure and the midline shift were not different among the groups. Hospital stays were less among patients who underwent IST, but did not reach statistical significance. Other secondary outcomes, namely, recurrence and death, were insignificant across the groups.

Table 3 shows a comparison of the characteristics of patients with good and poor outcomes at 3 months. There was no significant difference in indications for the procedure or the type of procedure between patients who had and did not have good outcomes. We performed regression analysis to determine the factors predicting good outcomes in patients undergoing EVT for CVST. We found that GCS >9 before the procedure, midline shift of <5 mm, and double vision predicted better outcomes at 3 months. Furthermore, we calculated Receiver operating characteristics - Area under the curve, which showed that GCS at baseline could predict the outcome at 3 months with an AUC of 0.85 (95% confidence interval: 0.74–0.96, *P* < 0.001). The rest of the variables were not different between the groups.

Table 1: Baseline patient characteristics

Parameters	Description (*n*=52)
Gender- male, *n* (%)	28 (53.8)
Age (years)	33.3±12.3
Clinical symptoms, *n* (%)	
Headache	44 (84.6)
Seizure	24 (46.1)
Altered sensorium	16 (30.7)
Hemiparesis	12 (23.07)
Double vision	8 (15.3)
Vision blurring	1 (1.9)
Clinical syndrome, *n* (%)	
Raised ICT syndrome	18 (34.6)
Encephalopathy	17 (32.6)
Focal neurologic deficit	14 (26.9)
Median duration of symptoms (days)	4 (3–7)
Risk factors, *n* (%)	
Hyperhomocysteinemia	13 (25)
Anemia	13 (25)
Vit B12 deficiency	11 (21.6)
OCP consumption	7 (13.5)
Polycythemia	7 (13.5)
APLA syndrome	5 (9.6)
Alcohol consumption	4 (7.7)
Postpartum	4 (7.7)
Dehydration	3 (5.8)
Malignancy	2 (3.9)
Mean GCS before the procedure (SD)	9.2 (4.1)
Mean midline shift in millimeters (SD)	2.8 (3.6)
Indication for EVT, *n* (%)	
Worsening of sensorium	21 (40.3)
Non-improvement of symptoms	15 (28.8)
Status epilepticus	6 (11.5)
Worsening of headache	3 (5.8)
Worsening of power	2 (3.8)
Vision loss	1 (1.9)
Median timing of EVT (in days)	6 (4–9)
Type of EVT, *n* (%)	
In situ thrombolysis	25 (48.1)
Mechanical thromboaspiration	16 (30.8)
Mechanical thromboaspiration with *in situ* thrombolysis	11 (21.2)
Median duration of hospital stay (days)	15 (9–29)

For categorical variables, frequency and percentage were used. For continuous variables, mean and SD or median with interquartile range was used. EVT = Endovascular treatment, GCS = Glasgow Coma Scale, SD = Standard deviation

Table 2: Comparison of variables among the three procedures

Variable	*In situ* thrombolysis (*n*=25)	Mechanical thromboaspiration (*n*=16)	Combination (*n*=11)	*P*
Duration of hospital stay, median (IQR)	12 (7.75–21)	15 (11.5–28.75)	21 (10–31)	0.6
Recurrence, *n* (%)	0	1 (6.2)	1 (9.1)	0.4
Angiographic outcome, *n* (%)				
Partial recanalization	18 (72)	7 (43.8)	6 (54.5)	0.01*
Near-complete recanalization	2 (8)	9 (56.2)	4 (36.4)	
Complete recanalization	4 (16)	0	1 (9.1)	
Death, *n* (%)	2 (8)	4 (25)	2 (18.2)	0.35
mRS <2 at 3 months, *n* (%)	20 (90.9)	10 (62.5)	6 (54.5)	0.04*
mRS <2 at discharge, *n* (%)	8 (36.3)	6 (37.5%)	1 (9.1)	0.21
Mean GCS before the procedure (SD)	10.4 (4.1)	9.13 (4.5)	6.9 (2.3)	0.06
Mean midline shift in millimeters before the procedure (SD)	1.9 (2.7)	4.1 (4.1)	2.7 (4.1)	0.17

Statistical test: Chi-square/Fischer's exact test was used for categorical variables. ANOVA was used for continuous variables. *$P<0.05$ considered statistically significant. ANOVA = Analysis of variance, GCS = Glasgow Coma Scale, mRS = Modified Rankin Scale, SD = Standard deviation

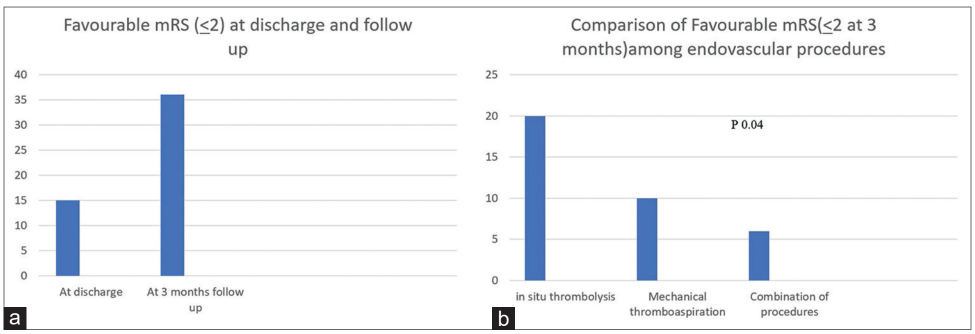

Figure 2: (a) mRS improvement between the time of discharge and 3 months follow-up. (b) Comparison of favorable mRS among the three procedures. mRS = Modified Rankin Scale

Those with poor outcomes at 3 months had a higher frequency of baseline GCS <9 (92.3% vs. 30.6%, $P < 0.001$) and midline shift >5 mm (46.2% vs. 11.1%, $P = 0.01$). We also tried to determine the factors predicting excellent and poor outcomes at the time of discharge. Poor outcomes at discharge were linked to female gender, having an altered sensorium, having an encephalopathic syndrome at presentation, having a parenchymal bleed, and having a midline shift [Supplement Table 1]. It is interesting to note that the duration of symptoms, the day of the procedure, and the age of the thrombus were not associated with the patient outcome.

Discussion

CVST is a treatable condition that would be potentially fatal without treatment.[6] Many case reports in the literature describe EVT for CVT, but there are only a few retrospective and prospective studies. To date, only one randomized controlled trial has been published that did not show a difference in outcome between the medical and interventional arms.[7]

In our study, it was observed that a significantly high number of patients had good outcomes with intervention. We further observed that patients who underwent IST had a substantially better outcome at 3 months than those who underwent other interventions. IST also achieved significantly better recanalization than other procedures. We identified midline shifts <5 mm and GCS >9 before the procedure as predictors of good outcomes. Variables such as encephalopathic syndrome, altered sensorium, mass effect, midline shift, parenchymal bleed, and female gender predicted poor outcomes at discharge, but none of the factors were associated with poor outcomes at 3 months. GCS, before the procedure, was able to predict the outcome at 3 months. Our study is one of the largest retrospective studies analyzing the effectiveness of EVT in refractory CVST.

The overall recanalization rate of 73% is concordant with the literature.[8,9] The outcomes of our research, which demonstrate enhanced recanalization using IST, align with the findings of Mohammadian *et al.*[10] and Siddiqui *et al*.[11] The reason could be that prolonged and continuous action of the thrombolytic drug that is delivered in the clot could have resulted in better resolution of the clot. Even though mechanical thromboaspiration aspirates clots, it would make it difficult to clear the entire clot burden and it may injure the endothelium, contributing to Virchow's triad. A smaller midline shift and a good GCS (>9) predicted good outcomes, which implies that patients with good sensorium perform better after the procedure. The presence of double vision was one of the factors predicting good outcomes in our study.

Table 3: Comparison of variables between patients with good and poor outcomes (at 3 months)

Variables	mRS ≤2 (*n*=36)	mRS >2 (*n*=13)	*P*
Age in years, mean ± SD	31.4±11.3	39.4±14.7	0.06
Gender- male, *n* (%)	21 (58.3)	7 (53.8)	0.77
Double vision, *n* (%)	8 (22.2)	0	0.05*
Raised ICT syndrome, *n* (%)	16 (44.4)	2 (15.4)	0.12
Encephalopathy, *n* (%)	10 (27.8)	7 (53.8)	
Focal neurologic deficit, *n* (%)	10 (27.8)	4 (30.8)	
Glasgow Coma Scale <9, *n* (%)	11 (30.6)	12 (92.3)	<0.001*
Midline shift >5 mm, *n* (%)	4 (11.1)	6 (46.2)	0.01*
Indication for EVT, *n* (%)			
Worsening of headache	3 (8.3)	0	0.46
Worsening of sensorium	14 (38.9)	7 (53.8)	
Worsening of power	2 (5.5)	0	
Non-improvement of symptoms	12 (33.3)	3 (23.1)	
Status epilepticus	3 (8.3)	3 (23.1)	
Vision loss	1 (2.8)	0	
Sinuses thromboses, *n* (%)			
Superior sagittal sinus	32 (88.9)	10 (76.9)	0.32
Transverse sinus	23 (63.9)	6 (46.2)	0.21
Sigmoid sinus	22 (61.1)	5 (38.5)	0.13
Deep sinuses	5 (13.9)	3 (23.1)	0.46
Parenchymal bleed	23 (63.9)	11 (84.6)	0.3
Midline shift	13 (37.1)	8 (61.5)	0.13
Mass effect	22 (61.1)	11 (84.6)	0.28
Age of thrombus, *n* (%)			
Acute	17 (47.2)	9 (69.2)	0.31
Subacute	17 (47.2)	3 (23.1)	
Chronic	2 (5.6)	1 (7.7)	
Angiographic outcome, *n* (%)			
Partial recanalization	21 (58.3)	7 (53.8)	0.95
Near-total recanalization	11 (30.6)	4 (30.7)	
Complete recanalization	4 (11.1)	1 (7.7)	
Long-term anticoagulation, *n* (%)			
Warfarin	15 (41.7)	4 (30.8)	0.06
Acitrom	13 (36.1)	3 (23.1)	
Dabigatran	8 (22.2)	3 (23.1)	
Apixaban	0	1 (7.7)	
Median duration of symptoms (days)	5 (3–7)	3 (1.5–6.5)	0.26
Median timing of EVT (days)	7 (4–9)	4 (3.5–7.5)	0.13
Median duration of hospital stay	14 (9–30)	18 (11–28)	0.42

Statistical test used: Chi-square test/Fischer's exact test for categorical variables and Mann–Whitney U test for continuous variables. *P<0.05 considered statistically significant. EVT = Endovascular treatment, mRS = Modified Rankin Scale

It could be related to the better sensorium of the patients who were able to come out with that symptom than those who were not. Contrary to the findings of Alwan *et al*.,[8] we identified GCS <9 and midline shift >5 mm as predictors of bad outcomes. Multiple unfavorable prognostic indicators were noted at the time of discharge, such as altered sensorium, encephalopathic syndrome, and parenchymal bleeding. However, none of these characteristics predicted unfavorable outcomes at the 3-month follow-up.[8] The reason could be the natural history of recovery itself. Unlike some studies, we found good outcomes, irrespective of the occlusion site.[9] The death rates in our study are in line with those reported in previous publications.[12,13]

Our study is one of the few studies in literature that tried to compare the various endovascular procedures. This study also has an adequate sample size for a rare disease. The limitations of our study include its retrospective trial design and recall bias, which the patient would have experienced during telephonic follow-up. The nonsignificant results regarding the outcome variables are likely to be due to a small number of patients in the poor outcome group.

Conclusion

We identified IST as a better, safe, and effective treatment for patients with refractory CVST. Even though there are no guidelines at present, EVT is effective in drug-refractory CVST. Patients with midline shift <5 mm and GCS of >9 may be good candidates for the procedure. These results need validation by adequately powered, intelligently designed randomized trials.

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Nonstandard abbreviations and acronyms

CVST- cerebral venous sinus thrombosis; EVT- endovascular treatment; rTPA- recombinant tissue plasminogen activator; ISCVST- International Cerebral Vein Thrombosis Study; OR- odds ratio.

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Conflicts of interest

There are no conflicts of interest.

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Supplementary Table 1: Comparison of variables at discharge between patients with good and poor outcomes

Variables	mRS <2 (n=15)	mRS >2 (n=34)	P
Male gender, n (%)	12 (80)	16 (47.1)	0.03*
Double vision, n (%)	5 (35.7)	3 (9.1)	0.02*
Altered sensorium, n (%)	1 (7.1)	15 (44.1)	0.01*
Raised intracranial tension syndrome, n (%)	8 (53.3)	10 (29.4)	0.02*
Encephalopathy, n (%)	1 (6.7)	16 (47.1)	
Focal neurologic deficit, n (%)	6 (40)	8 (23.5)	
Parenchymal bleed, n (%)	8 (53.3)	26 (81.2)	0.04*
Midline shift, n (%)	3 (20)	18 (54.5)	0.03*

*P<0.05 considered statistically significant. mRS = Modified Rankin Scale