Original Article

Intrasinus thrombolysis in cerebral venous sinus thrombosis: Experience from a university hospital, India

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Abstract

Background: Intrasinus thrombolysis (IST) is believed to improve outcome in patients of cerebral venous sinus thrombosis (CVST) unresponsive to heparin. **Purpose:** The purpose of this article is to describe our experience with IST in patients of CVST unresponsive to heparin. **Materials and Methods:** Hospital databases were searched, and patients with CVST who underwent IST from May 2011 to March 2014 were identified. Data on clinical presentation, duration of symptoms, and indications and dosage of IST were retrieved and outcomes analyzed. **Results:** Twenty-four patients received IST. The presenting symptoms included headache (n = 19), seizures (n = 16), and altered sensorium (n = 14); signs included papilledema (n = 20) and hemiparesis (n = 15). Nineteen patients received unfractionated heparin (UFH), four received low-molecular-weight heparin (LMWH), and one received both. In one patient, microcatheter could not be passed, two patients bled intracranially, and three had nonintracranial bleeds. Among four deaths, none was due to iatrogenic bleeding. On discharge, 10 patients (43.5%) had good improvement with the modified Rankin Scale (score; mRS) ≤2 and eight (34.8%) had partial improvement with mRS = 3, 4. Seventeen patients (73.9%) had mRS ≤2 at 6 months follow-up. Bleeding complications of urokinase were less than those of alteplase. Recanalization of the involved sinuses was achieved in all. Early intervention led to successful recanalization. Functional recanalization decreased intracranial bleeding. **Conclusion:** Till date, our study is the largest series of IST in CVST reported from India. IST may be more effective than systemic heparin anticoagulation in moribund and unresponsive patients despite the potential for bleeding manifestations. Functional recanalization is adequate for good results. However, a randomized prospective study comparing heparin anticoagulation with IST is warranted.

Key Words

Cerebral venous sinus thrombosis (CVST), intrasinus thrombolysis (IST), outcome

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Introduction

Cerebral venous sinus thrombosis (CVST) as a fatal entity was discovered on autopsy by Ribes *et al*. in 1825. Following advances in noninvasive neuroimaging techniques, CVST has been more frequently detected and it accounts for 0.5-1% of all strokes. It is considered to be one of the most common causes of stroke in the young.[1] Although most patients respond very well to treatment with heparin, some patients have a very stormy course with subsequent mortality. The subgroup of patients with poor outcome are those with coma, intracerebral hemorrhage (ICH), rapidly progressing clinical deficits, posterior fossa lesions, and involvement of the deep venous system.[2-4] Approximately 30% of patients with one or more of these risk factors had poor outcome despite treatment with heparin.[5] For these patients, endovascular thrombolysis might give better results.

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Aim

The purpose of this study is to describe the clinical presentation of a series of patients with CVST treated at our institute and to discuss the role and outcome of local thrombolysis.

Materials and Methods

Collection of data

Our hospital databases were searched and patients with CVST who had undergone intrasinus thrombolysis (IST) at our institution from May 2011 to March 2014 were identified. Medical records and imaging studies were reviewed retrospectively. Data on clinical presentation, predisposing conditions, imaging findings, time taken from the symptom onset to thrombolysis, duration of treatment with anticoagulation [anticoagulation with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) was the initial treatment in all the patients], initiation of thrombolytic therapy, dose of thrombolytic, duration of therapy, and clinical and radiological outcomes were collected.

The protocol used for this study was approved by the Institutional Review Board of Nizam's Institute of Medical Sciences, Hyderabad.

Indication for thrombolysis in all the cases was poor clinical condition of the patient at admission, rapid clinical deterioration including vision, or unresponsiveness to heparin.

IST procedure

Using the transfemoral approach, cerebral venogram was performed and individual sinuses were selectively catheterized. Depending on the availability of drugs, either urokinase (bolus of 100,000 IU and continued at a rate of 70,000-80,000 IU/h) or alteplase (bolus of 10 mg and continued at a rate of 1 mg/h)[6,7] was given until functional recanalization of the involved dural venous sinuses was achieved, to a maximum of 3 days. Appearance of bleeding manifestations led to prompt cessation of the therapy. Check angiograms were performed at 12-h intervals till termination.[8] Mechanical thrombectomy was not attempted in any of these patients.

Heparin was continued after thrombolytic therapy, and the dose was adjusted to maintain activated partial thromboplastin time (aPTT) at 2-3 times of normal levels. All patients were subsequently started on long-term oral anticoagulation (warfarin therapy) with target international normalized ratio (INR) of 2-3, which was continued for 6 months.

Outcome analysis

Clinical outcomes analyzed included short-term mortality, complications, and functional outcome as assessed by modified Rankin Scale score (assessed at the time of admission, discharge, and during follow-up at 6 months). Treatment response was assessed as good improvement (mRS 0, 1, 2), partial improvement (mRS 3, 4), or poor outcome (mRS 5, 6).

Radiological outcome was assessed during pre- and postthrombolysis states on digital subtraction angiography (DSA) using the Rabinstein score,[9] a CVST scoring system designed to quantify the distribution of the clot. This scale assigns 1 point for each involved sinus, internal cerebral vein, the vein of Galen, and for each third of the superior sagittal sinus; the maximum score is 10.

Results

Twenty-four patients were identified over a period of 3 years with a mean age of 30.5 years (16-70 years), of whom 12 were male. The median number of days between onset of symptoms and arrival at the hospital was 4 (range 2-45 days). Diagnosis in all patients was done within the first hour of arrival at the hospital, and anticoagulation was resorted to immediately. The median number of days between diagnosis and thrombolysis was 2 (range 3 h to 12 days). The average duration of hospitalization was 15 days.

Observations from our study are summarized in Table 1 (clinical presentation), Table 2 (risk factors), Table 3 (dural sinus involved) and Table 4 (treatment and outcome).

Sixteen patients had intracranial parenchymal lesions, and of them 14 had hemorrhagic and two had nonhemorrhagic venous

Table 1: Clinical presentation

Symptoms	Number of patients (%)
Headache	19 (79.1)
Seizures	16 (66.67)
Vomiting	16 (66.67)
Altered sensorium	14 (58.3)
Hemiparesis	15 (62.5)
Visual loss	3 (12.5)
Double vision	1 (4.16)
Signs	
Papilledema	20 (83.3)
Hemiparesis and seventh nerve palsy	15 (62.5)
Sixth nerve palsy	4 (16.67)
Third nerve palsy	2 (8.3)
Aphasia	5 (20.83)

Table 2: Risk factors

Risk factors	Number of patients (%)
Homocysteine	7 (29.1)
Alcoholism	6 (25)
Anaemia	6 (25)
Anticardiolipin antibodies	2 (8.3)
Oral contraceptives	3 (12.5)
Intrauterine death: sepsis	1 (4.1)
No risk factor identified*	6 (25)

*Other risk factors looked for, in all of our patients, are polycythemia, vasculitis, trauma, human immunodeficiency virus (HIV), infections, malignancy, nephrotic syndrome, drugs other than oral contraceptive pills (OCPs), protein C, S, AT III deficiency, factor V Leiden, prothrombin 20210 A mutation, postpartum status and past history of Deep venous thrombosis/ Pulmonary thromboembolism/ CVST; none was found to be positive

infarcts. Nine of the 14 patients with hemorrhagic venous infarcts had mass effect.

Treatment and outcome

Nineteen patients received UFH, four patients received LMWH, and one received both, before receiving local thrombolysis. All received heparin for a median period of 2 days (range 10 h to 12 days); the dose was adjusted to maintain aPTT at 2-3 times of normal levels. Duration of anticoagulation before IST was individualized on the basis of clinical status or symptomatic improvement/deterioration after anticoagulation. IST was chosen in those who had poor Glasgow Coma Scale (GCS) scores at admission ($n = 4$), rapidly progressing vision loss ($n = 1$), rapid deterioration after admission ($n = 6$)—these 11 patients were given IST without awaiting the effect of anticoagulation. Further 13 patients were those who did not respond and/or worsen neurologically despite optimal heparin therapy. The procedure was abandoned in one patient as the catheter could not be passed through the thrombus due to chronicity (duration of the disease was 45 days). Fifteen patients received alteplase [tissue plasminogen activator (tPA)] and eight received urokinase. The maximum dose of tPA was 82 mg (range 20-82 mg) and that of urokinase was 72 million IU (range 8-72 million IU). Only three of nine patients of intracranial venous infarcts

Table 3: Dural sinus involvement in patients with CVST

Sinus involved	Number of patients (%)
SSS* alone	1 (4.1)
SSS+Unilateral (TS)#	5 (20.8)
SSS+Unilateral (TS+Sigmoid)	5 (20.8)
SSS+Unilateral (TS+Sigmoid+IJVΦ)	1 (4.1)
SSS+Bilateral TS+Unilateral (Sigmoid+IJV)	2 (8.3)
Superficial and deep	10 (41.6)

*Superior Sagittal Sinus, #Transverse Sinus, ΦInternal Jugular Vein

Table 4: Treatment and outcome

Treated cases	Duration of heparin therapy (days)	Symptoms to IST (days)	Thrombolytic used	Clinical outcome				Radiological outcome (Rab score)#	
				mRS‡‡			Complication		
				At admission	At discharge	At 6 months		Pre IST	Post IST
Unresponsive to heparin									
Case 1	10*	14	tPA	2	0	0		7	0
Case 2	4*	14	tPA	2	1	0		3	0
Case 3	2*	5	tPA	5	3	0	DVT	3	1
Case 4	12*	42	Urokinase	4	0	0		4	0‖
Case 5	7†	37	tPA	4	1	1	Multiple IC††+GIT bleeds	3	0‖
Case 6	3*	17	tPA	5	2	1		5 (abandoned)	
Case 7	2*	6	Urokinase	5	2	0	DVT	6	2
Case 8	2†	5	tPA	5	4	1	Local and Tracheal bleed	8	0
Case 9	9*	12	tPA	5	4	2		2	0‖
Case 18	3*	13	Urokinase	5	3	1	Local bleed	3	0
Case 19	5*	7	tPA	5	4	3		6	2
Case 21	10*†	15	Urokinase	5	5	2	VAP‡	5	1
Case 22	2*	6	Urokinase	5	6		IUD¶-Sepsis-DIC**-Death	5	1
Poor GCS at admission									
Case 10	1*	46	tPA	5	6		Death	5 (check angio not done)	
Case 11	0.42*	4.42	tPA	5	1	0		10	1
Case 12	2*	6	tPA	5	4	3		5	2
Case 20	0.42*	4.42	tPA	5	5	2	††IC bleed, VAP‡, UTI§	5	1 Almost‖
Rapid deterioration after admission									
Case 13	1*	3	Urokinase	2	0	0	VAP‡	8	4
Case 14	2*	6	tPA	5	0	0		8	3
Case 16	3.5*	6.5	tPA	5	6		Local, gum bleed and hematuria, death	3	1
Case 17	0.13†	4.13	tPA	5	6		Death: sepsis	3	0
Case 23	1*	4	Urokinase	4	4	0	UTI§	2	0‖
Case 24	1†	3	Urokinase	4	2	0		4	2
Rapidly progressing vision loss									
Case 15	0.42*	10.42	tPA	5	4	1		4	1

*Unfractionated heparin, †Low-molecular-weight heparin, ‡Ventilator-associated pneumonia, §Urinary tract infection, ‖Complete recanalization, ¶Intrauterine death, **Disseminated intravascular coagulation, ††Intracranial, ‡‡Modified Rankin Scale (score), #Radiological outcome was assessed using Rabinstein score on DSA

with mass effect underwent decompressive craniectomy as the primary intervention.

At the time of discharge, 10 patients (43.5%) had good improvement with mRS <2, while eight (34.8%) had partial improvement, two (8.7%) had mRS scores of 5, and four (17.4%) died. Five of 23 patients had bleeding complications, among whom four had received tPA and one was on urokinase. Two among these five patients had multiple intracranial bleeds while on tPA intrasinus infusion. However, they recovered following the stopping of the infusion and were discharged after 1 week in stable condition. Of the four deaths, two were due to transtentorial herniation due to expanding venous infarcts and the other two were due to sepsis. Seventeen of 23 patients (73.9%) had mRS ≤2 at 6 months follow-up.

In our study, recanalization was documented in 22 (complete in four, partial in 18) patients who received IST. One patient died even before the first check angiogram could be performed.

Illustrative case

Case 1

A 20-year-old farmer presented with altered sensorium and seizures since 2 days; clinical evaluation revealed hypotension, GCS 3, and sluggish doll's eye movement. He was intubated and mechanically ventilated with adequate hemodynamic support. On DSA [Figure 1], all superficial sinuses and the deep venous system were thrombosed. His GCS improved to E3 M6 V4 after 24 h of immediate intrasinus thrombolytic infusion (received a total of 70 mg of tPA). He was discharged in stable condition without any neurological deficit.

Discussion

The utility of IST as a treatment modality in CVST patients has been extensively reviewed in the literature.[10-16] The theoretical advantage of IST for CVST is that the drug is delivered where needed, thus decreasing the incidence of bleeding manifestations and increasing the efficacy of the thrombolytic agent.

So far, our study has been the largest from India. Moreover, both tPA and urokinase were used as thrombolytic agents in different subjects, providing an opportunity to have experience with both. In our study, 17 of 23 patients (73.9%) had mRS ≤2 at 6 months follow-up—at par with the previous series,[6,17] but at the time of discharge, only 10 patients (43.5%) had good improvement with mRS <2. This is probably because of the large proportion of patients with a moderate to large hemorrhagic component (n = 14) among those with venous infarcts (n = 16), and many patients with deep venous system involvement (n = 10), which is very high when compared to the previous series.[6,11,14] Despite this huge proportion of hemorrhagic infarcts, none of our patients developed iatrogenic expansion of the hematoma with the IST. Five patients developed bleeding manifestations as a complication of therapy, two of whom bled intracranially. Others also showed similar rates of hemorrhage.[6,14] Both bleeds occurred in those patients treated with intrasinus tPA having complete or near complete recanalization of the involved sinuses. In our series, intracranial bleeding did not occur with urokinase infusion, suggesting less bleeding complications with the use of urokinase while similar efficacy is maintained to tPA—time to restore patency of sinuses with usage of urokinase (average = 40 h) was more or less equal to that of tPA (average = 35 h). Bleeding had been more with tPA probably because of its higher potency, despite clot specificity. Two of the four deaths in this study were due to transtentorial herniation, the other two were related to sepsis. There were two deaths reported in one series and one in another series from iatrogenic ICH,[6,17] in contrast to no deaths in our study.

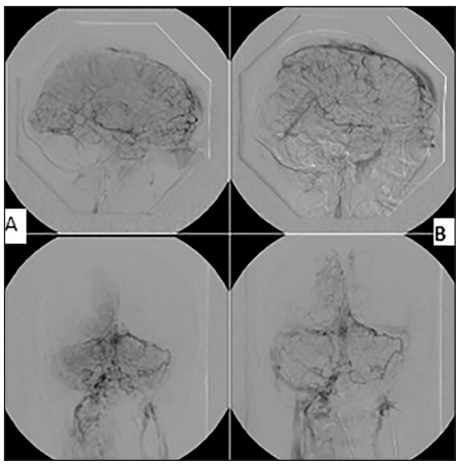

Figure 1: DSA of the illustrative case (a) Prethrombolysis (b) Postthrombolysis

Recanalization was documented in all of our patients receiving IST, while others showed a recanalization rate of 63-75%.[6,14] There is no correlation between extent of recanalization and clinical outcome, i.e., partial or functional recanalization scores higher over complete recanalization of sinuses for CVST, lessening the thrombolytic dosage and bleeding complications. Death and disability appear to be primarily related to the extent and swiftness of onset of the sinus thrombosis and venous infarctions. Six of nine patients with venous infarcts and mass effect who did not undergo decompressive craniectomy had prolonged hospital stay with increased morbidity and mortality. Three of these nine patients underwent both IST and decompression, and made a faster recovery. IST and decompressive craniectomy were complementary in these patients.

However, in the absence of randomized controlled trials, the exact role of IST in the management of cerebral venous and sinus thrombosis is unclear, especially with regard to patient selection and optimal time to intervene. There are no established criteria in the literature regarding indications for thrombolysis in CVST. The criteria for IST in this study were rapid worsening of symptoms or lack of response to systemic anticoagulation. Early therapeutic intervention may lead to successful recanalization of the involved sinuses.

Conclusion

CVST can be fatal or disabling if untreated, and even with systemic anticoagulation the condition may progress. Heparin remains the first-line treatment because of its efficacy, safety, and feasibility. The adjunction of local thrombolysis is indicated in the rare cases where rapid deterioration occurs

despite adequate anticoagulation. Urokinase may be a safe and preferred thrombolytic agent. Functional rather than complete recanalization is adequate for achieving good results. The uncertain natural history, multiplicity of causes, and variable severity of clinical presentation result in current management being "case by case."

Conclusions about optimal treatment in CVST patients cannot be drawn based on our study alone as it was not randomized, had a small sample size, no head-to-head comparisons were made between subgroups receiving tPA and urokinase, and there was no set control group treated with heparin alone. Nevertheless, our study highlights potential role of IST in a subset of CVST patients.

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Conflicts of interest
There are no conflicts of interest.

References

1. Bousser MG, Ferro JM. Cerebral venous thrombosis: An update. Lancet Neurol 2007;6:162-70.
2. Canhao P, Ferro JM, Lindgren AG, Bousser MG, Stam J, Barinagarrementeria F; ISCVT Investigators. Causes and predictors of death in cerebral venous thrombosis. Stroke 2005;36:1720-5.
3. de Bruijn SF, de Haan RJ, Stam J. Clinical features and prognostic factors of cerebral venous and sinus thrombosis in a prospective series of 59 patients. For The Cerebral Venous Sinus Thrombosis Study Group. J Neurol Neurosurg Psychiatry 2001;70:105-8.
4. Spearman MP, Jungreis CA, Wehner JJ, Gerszten PC, Welch WC. Endovascular thrombolysis in deep cerebral venous thrombosis. AJNR Am J Neuroradiol 1997;18:502-6.
5. Rahman M, Velat GJ, Hoh BL, Mocco J. Direct thrombolysis for cerebral venous sinus thrombosis. Neurosurg Focus 2009;27:E7.
6. Kumar S, Rajshekher G, Reddy CR, Venkateswarlu J, Prabhakar S. Intrasinus thrombolysis in cerebral venous sinus thrombosis: Single-center experience in 19 patients. Neurol India 2010;58: 225-9.
7. Sood N, Sood N, Talkad A. A case of worsening deep cerebral venous sinus thrombosis managed by intrasinus thrombolysis. Case Rep Neurol Med 2011;2011:272841.
8. Waugh J, Plumb P, Rollins N, Dowling MM. Prolonged direct catheter thrombolysis of cerebral venous sinus thrombosis in children: A case series. J Child Neurol 2011;27,3:337-45.
9. Zubkov AY, McBane RD, Brown RD, Rabinstein AA. Brain lesions in cerebral venous sinus thrombosis. Stroke 2009;40:1509-11.
10. Scott JA, Pascuzzi RM, Hall PV, Becker GJ. Treatment of dural sinus thrombosis with local urokinase infusion. Case report. J Neurosurg 1988;68:284-7.
11. Horowitz M, Purdy P, Unwin H, Carstens G 3rd, Greenlee R, Hise J, *et al*. Treatment of dural sinus thrombosis using Selective catheterisation and urokinase. Ann Neurol 1995;38:58-67.
12. Smith TP, Higashida RT, Barnwell SL, Halbach VV, Dowd CF, Fraser KW, *et al*. Treatment of dural sinus thrombosis by urokinase infusion. Am J Neuroradiol 1994;15:801-7.
13. Kim SY, Suh JH. Direct endovascular thrombolytic therapy for dural sinus thrombosis: Infusion of alteplase. AJNR Am J Neuroradiol 1997;18:639-64.
14. Frey JL, Muro GJ, McDougall CG, Dean BL, Jahnke HK. Cerebral venous thrombosis: Combnined intrathrombus rtPA and intravenous heparin. Stroke 1999;30:489-94.
15. Canhao P, Falcao F, Ferro JM. Thrombolytics for cerebral venous thrombosis: A systematic review. Cerebrovasc Dis 2003;15: 159-66.
16. Tsai FY, Kostanian V, Rivera M, Lee KW, Chen CC, Nguyen TH. Cerebral venous congestion as indication for thrombolytic treatment. Cardiovasc Intervent Radiol 2007;30:675-87.
17. Stam J, Majoie CB, van Delden OM, van Lienden KP, Reekers JA. Endovascular thrombectomy and thrombolysis for severe cerebral sinus thrombosis: A prospective study. Stroke 2008;39:1487-90.