Heparin or Local Thrombolysis in the Management of Cerebral Venous Sinus Thrombosis?

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Summary

Patients with acute cerebral venous sinus thrombosis treated with Heparin or in situ thrombolysis in our department were evaluated in an attempt to rationalize treatment with heparin or thrombolysis. 279 patients with angiographically proven acute cerebral venous sinus thrombosis were included in the study. Patients were classified into mild and severe clinical grade. The study was divided into three phases. Phase I included 27 patients treated with systemic heparin. Phase II included 72 patients, 30 in severe grade and 42 in mild. 26 were thrombolysed with 14 in severe and 12 in mild grade. Phase III included 180 patients treated according to a defined protocol. 133 were in mild grade and 47 in severe. 67 patients were thrombolysed. In the thrombolysed group 27 patients were in mild grade and 40 in severe. 113 patients were treated with systemic heparin. Following acute management all were anticoagulated for six months.

The baseline characteristics were found to be same in all three phases. On comparison of outcome in Phase III with Phase I the likelihood ratio was found to be statistically significant in favor of Phase III ($p < 0.0001$). The likelihood ratio was found to be statistically significant in mild and severe clinical grade in favor of thrombolysis in Phase III ($p 0.039$ in mild and $p 0.00001$ in Severe clinical grade). This ratio

was insignificant ($p = 0.716$) for intracranial bleed; however, local puncture site bleeding was found to be significant in the thrombolysed group (0.00005).

Introduction

Venous strokes include the clinical condition arising from thrombosis of the cerebral dural venous sinus and the superficial and deep venous system. Occlusion of cerebral venous drainage leads to a backpressure effect causing hemorrhagic venous infarcts resulting in focal neurological deficit and raised intracranial pressure. Cerebrospinal fluid is normally absorbed by arachnoid villi into the dural sinuses. Failure of CSF absorption due to high venous pressure leads to a further increase in intracranial pressure^{1,2}. The disease has varied presentation and varied outcome. It is common in the Indian subcontinent and accounts for 10-20% of all young strokes in India^{3,4}. The outcome of cerebral venous sinus thrombosis is unpredictable but it is far better than that of arterial stroke once the acute phase is over.

Two randomized trials on heparin (Enhaupl et al.) reported a significant decrease in morbidity and mortality in the heparin group^{5,6}. There is an absolute risk reduction in death and dependency by 14% and 15% and relative risk reduction by 70% and 56% respectively^{7,8}. A meta analysis of heparin in CVT concluded

that it has modest but clinically important benefit in the treatment. The mortality in most recent series is 10-20%, but patients with encephalopathy or impending encephalopathy do not have a good outcome with mortality up to 53%⁹⁻¹⁵. Attempts have been made to recanalize the sinus by chemical and recently by mechanical means¹⁶⁻¹⁹. In situ thrombolysis has been advocated in extreme cases. Here we present a large series of patients treated with heparin or local thrombolysis over eight years.

Material and Methods

The present study includes 279 patients treated in the medical neuro ICU and interventional neuroradiology department of our institute from 1995 to 2003. All patients had angiographically proven cerebral venous sinus thrombosis. The study is divided into three Phases (I, II and III). In Phase I (1995-1996) all patients were treated with systemic heparin. In Phase II (1997-1999) a few patients were taken

Table 1 **KEM INR Criteria for local thrombolysis for cerebral venous sinus thrombosis. (Based on clinical and DSA grades).**

Grade	Clinical Grading	DSA Grading
Grade 1	symptom free	Partial thrombosis of dural sinus with no restrictive venous outflow
Grade 2	minor symptoms (headache, vomiting, diplopia, seizures)	Dural sinus occlusion with no restrictive venous outflow.
Grade 3	major neurological deficit but fully responsive	Dural sinus occlusion with restrictive venous outflow.
Grade 4	impaired state of alertness but capable of protective or adaptive responses to noxious stimuli. (GCS 8-10)	Deep venous system occlusion.
Grade 5	poorly responsive, but with vital signs. (GCS 5-7)	Dural sinus and deep vein occlusion with restrictive venous outflow.
Grade 6	not responsive to shaking, non-adaptive response to stimuli and progressive instability of vital signs. (GCS 3-4)	
<i>Mild Clinical Grade: Clinical status 1 to 3 - Severe Clinical grade: Clinical status 4 to 6</i>		

Table 2 **Thrombolysed and heparin groups: 3 Phases.**

Phases	Clinical Group	Thrombolysed	heparin	Survival Thromb.	Survival heparin	Deaths Thromb.	Deaths heparin
Phase 1	Mild 17	—	17	—	13		04
27	Severe 10		10	—	0	—	10
Phase 2	Mild 42	12	30	12	28	0	02
72	Severe 30	14	16	06	04	08	12
Phase 3	Mild 133	27	106	27	99	0	07
180	Severe 47	40	07	26	0	14	07
<i>Thromb: thrombolysed with urokinase; figures: number of patients in each group</i>							

up for local thrombolysis. In Phase III (2000-2003) a prospective trial was carried out where patients were treated with heparin or local thrombolysis according to defined criteria based on clinical and digital subtraction angiography grades (table 1). CT grading was done to assess severity, progression and complications if any occurred. CT Grades were: Grade I: no parenchymal change (hyperdense sinuses, cortical veins, empty delta sign); Grade II: non hemorrhagic venous infarct without mass effect; Grade III: non-hemorrhagic infarct with mass effect; Grade IV: hemorrhagic venous infarct (max diameter <3 cm) with no mass effect; Grade V: hemorrhagic venous infarct (max diameter >3 cm) with mass effect.

In Phase I 27 patients of cerebral venous sinus thrombosis were seen. All patients were treated with systemic heparin according to the treatment paradigm. The mild clinical group included 17 patients and the severe clinical group ten patients according to clinical scale. (tables 2,4)

In Phase II of the 72 cases included, 42 were in mild and 30 patients in severe clinical grade. In some of these patients local thrombolytic therapy was advocated for the first time in our center. Twenty-six patients were treated with local thrombolytic therapy with urokinase. Twelve in the mild group and 14 in the severe group were lysed. These patients were thrombolysed as and when they were referred from the clinicians. No criteria for selection for thrombolysis were used (tables 2,3)

Phase III included 180 patients treated according to the designed protocol approved by the institutional ethics committee. All human participants gave their written informed consent to be included in the study (tables 2,4).

Inclusion criteria: Patients were taken for thrombolysis if they fulfilled the following criteria: a) Patients in severe clinical grade on admission^{4,6} with evidence of dural venous sinus thrombosis and restrictive venous outflow on cerebral angiogram; b) Patients in clinical grade 3 worsening on heparin therapy. Restriction to venous outflow was defined as an increase in brain circulation time >12 s, delay in the drainage of cortical veins with cortical veins hanging in space.

The remaining patients were treated with systemic heparin maintaining a twice normal PTT.

Figure 1 CT Scan: hemorrhagic venous infarct.

Exclusion criteria: Patients with major surgery or head injury (<6 weeks), gastrointestinal or genitourinary tract bleeding (<2 weeks), intracranial arteriovenous malformations, aneurysms or neoplasm's, bleeding diathesis, INR >1.7 or elevated aPTT, fewer than 100,000 platelets, were excluded from the study.

A detailed clinical and neurological examination was carried out for all patients. All subjects underwent a CT scan. On clinical and CT findings diagnosis of cerebral venous sinus thrombosis was suspected. Routine hematological, biochemical, bleeding profiles were done for all patients. These patients were subjected to cerebral angiography for confirmation of diagnosis and treatment if they fitted the inclusion criteria. They were treated either with heparin or selective thrombolysis with urokinase according to our selection criteria. All patients were shifted to the medical intensive care unit and strict neurological monitoring was done.

If any patient deteriorated an urgent CT brain scan was done to rule out progression of disease or fresh hemorrhage.

The urokinase infusion continued until the objectives were achieved or there was a complication. Medical treatment for seizures, raised intracranial tension or infections was given simultaneously. Systemic heparin was not given as

Figure 2 A) ICA angiogram venous phase showing thrombosis of SSS, Straight, and lateral sinuses. B) Mechanical clot maceration with glide wire.

long as urokinase infusion continued. After thrombolysis was stopped patients were treated with regular intravenous heparin infusion, followed by oral anticoagulation for six months.

Procedure: All procedures were done on digital subtraction angiogram (DSA). Phase I and II cases were done on Philips BV29 and Phase III cases were done on a Philips Allura integris. A cerebral angiogram with late venous phases was done in all patients (figures 2A,3B). Patients fulfilling the inclusion criteria were taken for thrombolysis. A femoral access was secured and a guiding catheter (Envoy 6F, Cordis) was placed in the jugular bulb. Mechanical clot maceration was done with the glide wire (figure 2B) (Terumo 38) following which a microcatheter (Excelsior, Prowler etc) was navigated and placed in the thrombosed segment of sinus confirmed on a selective venogram (figure 3A). Urokinase infusion was started at the rate of 60,000 to 100,000 units per hour. Periodic check venograms were done every 10h (figure 3A). The infusion was continued until brisk flow in the sinuses was achieved or a major complication occurred. Complications were defined as i) minor; puncture site bleeding ii) major; intracranial bleed, or peripheral bleed requiring transfusion. After thrombolysis all patients were subjected to oral anticoagulation for six months.

Results

Phase I

All 27 patients were treated with systemic heparin. 48.14% (13 patients) made a complete clinical recovery and a mortality rate of 51.85% (14 cases) was seen. Mortality was 100% (10 cases) in the severe clinical group. In the mild clinical grade, four patients (23.53%) out of 17 died and the remaining 13 made a clinical recovery (tables 2,4).

From Phase 1 we concluded that a) our system of assessing severity of disease is fairly reliable in predicting mortality. b) Patients grouped in severe clinical grade have a poor outcome on heparin therapy.

Phase II

In the second phase 72 patients were seen. In Phase II we thrombolysed patients without any defined criteria: 26 (36.11%) were subjected to local thrombolysis. In the thrombolysed group total survival was 69.23% (18 cases) out of which 7.69% (2 patients) had residual neurological deficits and there was a mortality rate was 30.77% (8 cases); 46 patients received systemic heparin. 69.57% (32 patients) made a complete clinical recovery and the mortality rate was 30.43% (14 patients). There was no mortality in patients of the mild clinical group who were lysed, whereas there was a mortality

Figure 3 A) Microcatheter in dural sinus. B) Post thrombolysis complete resolution of cortical and venous sinus thrombosis.

of 6.6% (2 cases) in mild clinical grade on heparin. In the severe manifestation group (30 patients) 14 were lysed. Clinical recovery was seen in six (42.86%) and there was mortality of eight (57.14%). In 16 patients of severe grade who were not thrombolysed the mortality was

75% (12 cases) and only 25% (4) made complete recovery (tables 2 and 3).

In this Phase the validity of our system to predict mortality was reconfirmed. In situ thrombolysis did not make any change in the outcome of patients in mild clinical grade how-

Table 3 **Phase II: comparison of thrombolysed and heparin groups.**

	Thrombolysed group	Heparin group
Age in yrs (Mean)	42.4	44.4
Sex (M:F)	2:1	1.7:1
Severe Grade (30 Pts.)	46.67% (14 pts.)	53.33% (16 pts.)
Mild Grade (42 Pts.)	28.57% (12 pts.)	71.43% (30 pts.)
CT Scan (Hemorrhagic Infarct)	40.44%	37.76%
DSA (Grade 3 to 5)	30.56%	21.22%
Major Bleed (On Treatment)	Nil	2.78%*
Survival	69.2%	69.5%
Death (Severe Grade)	57.14%	75%
Death (Mild Grade)	NIL	6.6%

*on anticoagulation.

ever there was trend towards decrease in mortality in severe clinical grade.

Phase III

Phase III included 180 patients with 111 men and 69 women. The male: female ratio was 1.6:1. Patients were in age groups ranging from four to 65 years. Most patients were young in the 4th decade. In 141 (78.53%) patients a risk factor was found. 85.5% were diagnosed within first two weeks of onset of symptoms. Duration of symptoms varied from a minimum of one day to a maximum of one month.

The commonest presenting features were headache and vomiting (70%), seizures (65%) and focal neurological deficits (53.33%); 26.11% patients were unconscious on admission.

In mild clinical grade (1-3) there were 133 (73.89%) patients (table 2). In severe clinical grade (4-6) there were 47 patients (26.11%). (table 2).

CT scan Grading: 84 patients (46.67%) were in CT grade IV and 55(30.56%) in grade V.

On cerebral angiography 86 patients (47.7%) were in DSA grade 3 and above. The most common dural sinus found to be thrombosed was the SSS (71.11%).

Sixty-eight patients (37.78%) out of the total 180 were included for thrombolysis. In the mild clinical group there were 133 patients and 27 were taken for local thrombolysis. In severe clinical grade 41 out of 47 were taken for local thrombolysis. All patients taken for thrombolysis in the mild group were in clinical grade 3. In the thrombolysed group of 27 patients in mild grade mortality was nil. In the non-thrombolysed group of 106 patients on heparin mortality was 6.6% (7 deaths). Patients had rapid clinical improvement in symptoms of headache, vomiting, diplopia and had control of seizures in the thrombolysed group. All patients thrombolysed were asymptomatic for headache and vomiting by 24 hours. Focal neurological deficits did not show any change until the infusion stopped but they had a complete motor recovery on follow-up.

In the severe clinical group there were 47 patients and 41 were taken up for thrombolysis as they fulfilled the inclusion criteria. Twenty-one patients were in clinical grade 4 (GCS 8-10) and 26 in clinical grade 5 (GCS 5-7). Forty patients were thrombolysed and there was one technical failure. Out of 40 patients thrombolysed 65% (26 patients) showed a dramatic im-

Table 4 Comparison of Phases I and III.

	Phase I	Phase III
Age in yrs (Mean)	41.52	46.67
Sex (Ratios)	1.4:1	1.6:1
Severe Clinical Grade	37.04%	26.11%
CT (Hemorrhagic Infarct)	80.71%	77.22%
DSA (Grade 3 to 5)	48.1%	47.78%
OUTCOME		
Major bleed (Intracranial)	Nil	2.99%
Death (Total)	51.85%	15.56%
Death (Severe Grade)	100%	35%*
Death (Mild Grade)	23.53%	6.6%**
Survival	48.15%	84.44%
* thrombolysed group; **non thrombolysed mild group		

provement on local thrombolysis. Fifty per cent (20 patients) made a recovery in consciousness level with a GCS 15/15 at the end of infusion. Maximum improvement was seen in the first 24 hours of infusion. Six patients (15%) showed a gradual improvement in level of consciousness even after recanalisation of the dural sinuses. Patients who had focal neurological deficit made a complete recovery on first follow-up at one month (MRS score 0) (table 3).

The total mortality in the severe clinical group was 44.68% (21 patients) and 35% (14 patients) of these were in the thrombolysed group. All deaths occurred within five days of onset of symptoms. Out of 14 patients, 12 patients (85.71%) died from mass effect of hemorrhagic venous infarct and irreversible diffuse brain damage because of prolonged severe raised intracranial pressure. These 12 patients had recanalisation of sinus on angiogram but did not show clinical recovery. Eight of these patients were in CT grade 5 and four in CT grade 4. Nine patients had bleeding complication. Two patients had intracranial bleed on urokinase infusions and died. Seven had mild puncture site oozing.

Seven patients in severe clinical grade were treated with systemic heparin. Mortality in the group of non-thrombolysed severe clinical grade was 100%. One patient fulfilled the inclusion criteria but could not be thrombolysed because of inability of the microcatheter to pierce tough thrombus.

The remaining six patients were in clinical grade 4 and DSA grade 2 so were excluded according to the protocol, as there was no restriction to venous outflow. These patients had a rapidly progressive downhill course and died within 48 hours.

There was no difficulty in mechanical clot maceration and microcatheter placement in patients presenting within the first week of presentation. It was technically difficult to position the microcatheter into the dural sinus in seven out of ten patients who presented late.

The average dose of Urokinase required for recanalisation was 2.4 million units. Average duration for recanalisation was 24h. Recanalisation of the sinuses and antegrade flow was restored in 97.01% of patients. The maximum dose of urokinase used was 8.5 million IU and the minimum required was 50,000 IU. The maximum duration of infusion was three days and 13 hours and the minimum was five hours.

It was seen that patients in the severe clinical grade when treated with local urokinase thrombolysis had a mortality of 35% against 100% in the non thrombolysed group.

Outcome

On statistical analysis the likelihood ratio of baseline characteristics were found to be the same. In Phases I and III age in years (p 0.869), gender (p 0.375), duration of symptoms in days (p 0.433), comparison was found to be not significant. The unpaired T test was found to be not significant on comparison of clinical grade (p 0.159), DSA grade (p 0.381) CT grade (p 0.141) and GCS on admission (p 0.265) in Phases I and III.

The likelihood ratio was found to be not significant on comparison of baseline characteristics in the thrombolysed group and heparin group in the severe clinical grade in Phase III, i.e. GCS on admission (p 0.152), clinical grade (p 0.072), CT grade (p 0.151 and DSA grade (p 0.426) were the same in both groups.

The likelihood ratio on comparison of outcome between the Phases I and III was found to be statistically significant with $p < 0.0001$. The likelihood ratio was found to be statistically significant in mild and severe clinical grade in favor of thrombolysis in Phase III (p 0.039 in mild and p 0.00001 in severe clinical grade). The likelihood ratio was found to be significant (p 0.005) on comparison of outcome in Phases I and II.

The likelihood ratio was insignificant (p 0.716) for intracranial bleed; however, local puncture site bleeding was found to be significant in thrombolysed group (p 0.00005).

Discussion

Our study confirmed that our clinical criteria are reliable to assess severity of the disease and predict mortality. Patients were divided into mild and severe clinical grade and patients grouped in severe clinical grade had significantly higher mortality in all three phases.

In situ thrombolysis could be advocated as first line therapy based on clinical and angiography criteria in severe clinical grade patients or patients with mild clinical grade deteriorating on heparin therapy. Patients who do not have adequate venous collaterals and have restrictive venous outflow have venous conges-

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tion, cerebral edema, hemorrhagic infarcts and raised intracranial pressure. Long-standing high intracranial venous pressure leads to irreversible brain damage²⁰. Our clinical and angiographic criteria helped to identify this group of patients and they were treated more aggressively. Hemorrhagic venous infarcts are not a contraindication for thrombolysis as in the phase III thrombolysed group 67.16% of patients had hemorrhagic venous infarcts.

The likelihood ratio on comparison of outcomes between Phases I and III showed that outcome was statistically significant with $p < 0.0001$. Total mortality in phase I was 51.85% and 30.5% in phase II when some patients were thrombolysed. This dropped to 15.56% in phase III. In Phase II there was a trend towards a decrease in mortality in severe clinical grade on thrombolysis versus medical therapy with heparin.

The likelihood ratio was found to be statistically significant in mild and severe clinical grade in favor of thrombolysis in Phase III. The mortality in severe clinical grade was 35% in the thrombolysed group against 100% in the heparin group. Seven patients in severe clinical grade were treated with systemic heparin. Mortality in the heparin group severe clinical grade was 100%. One patient fulfilled the inclusion criteria but could not be thrombolysed because of inability of the microcatheter to pierce tough thrombus. The remaining six patients were in clinical grade 4 and DSA grade 2 so were excluded according to the protocol, as there was

no restriction to venous outflow. These patients had a rapidly progressive downhill course and died within 48 hours.

The likelihood ratio was insignificant ($p = 0.716$) for intracranial bleed. However, local puncture site bleeding was found to be significant in the thrombolysed group ($p = 0.00005$).

Multiple small series show good results with thrombolytic therapy like ours, but no randomized trial has been done¹⁷. Previous studies from Horowitz who treated 13 patients with extensive thrombosis of several sinuses via trans-femoral route showed good results with sinus patency and good recovery in 12 patients²¹. Local thrombolytic therapy was done first by Scott et al. in 1988 via a frontal burr hole in patients with hemorrhagic infarct who recovered completely²². Kim and Suh used rtPA for local thrombolysis in nine patients with good results and no post treatment hemorrhages²³. Wasay et Al. reported 40 patients with superior sagittal sinus thrombosis treated with local urokinase thrombolytic therapy versus heparin and found that post treatment neurological function was better in the thrombolysed group¹⁶.

Conclusions

Our study confirms the validity of our clinical criteria to predict mortality. Patients in severe clinical grade have a poor outcome on heparin therapy. In situ thrombolysis is an effective form of management in patients with cerebral venous thrombosis in severe clinical grade.

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