

Original Article

Local thrombolytic therapy in severe cerebral venous sinus thrombosis during puerperium

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Abstract: This study is to explore and evaluate the efficacy and safety of local thrombolytic therapy in superior sagittal sinus in patients with severe cerebral venous sinus thrombosis during puerperium, as well as the efficacy and safety of anti-platelet aggregation treatment for preventing recurrence. Twelve patients during postpartum period with cerebral venous sinus thrombosis were received local thrombolytic therapy by placing a micro-catheter at the distal end of superior sagittal sinus from January 2008 to December 2013. All the patients accepted mechanical thrombus maceration before local intrasinus thrombolytic therapy, and were treated with low molecular weight heparin in the acute phase. After local thrombolytic therapy, anti-platelet aggregation treatment was performed for 6 months. Follow-up data included lumbar puncture, fundus examination and magnetic resonance venography (MRV) once per half year for 6-70 months. At discharge, the intracranial pressure of 12 patients reduced to below 200 mmH₂O. DSA or MRV confirmed that superior sagittal sinus of 9 patients were smooth. The cortex venous and deep venous were recovered to normal. Superior sagittal sinus of 3 patients recanalized partly. Cortex venous and deep venous was compensated. The follow-up study indicated that no thrombosis and new neurological symptoms occurred among all patients. Local thrombolytic treatment is safe and effective in patients with severe cerebral venous sinus thrombosis during puerperium. The collateral circulation compensation is the main recovery factor. And it is also safe and effective for anti-platelet aggregation treatment to prevent recurrence of cerebral venous sinus thrombosis.

Keywords: Puerperium, cerebral venous sinus thrombosis (CVST), superior sagittal sinus, intrasinus thrombolysis (IST), anti-platelet aggregation

Introduction

Cerebral venous sinus thrombosis (CVST) is an uncommon severe maternal complication during puerperium, with an incidence of 12/100 000 times of parturition [1]. Anticoagulant therapy with heparin or low molecular weight heparin is the primary treatment, rendering mortality lower but still lasting 5-30% [2, 3]. With the development of interventional radiology in neuroscience, intrasinus thrombolysis (IST), mechanical thrombus maceration, intraarterial thrombolysis and stenting have become an effective treatment to reduce the disability rate and mortality [4, 5].

Superior sagittal sinus thrombosis accounts for 70%-80% of CVST [5]. In this study, superior sagittal sinus was involved in all 12 cases. And the thrombus was found to be difficult to dis-

solve in a short time during IST. So, this study is to evaluate the efficacy and safety of local thrombolytic therapy in superior sagittal sinus in patients with severe CVST during puerperium, as well as the efficacy and safety of anti-platelet aggregation treatment for preventing recurrence.

Methods

Samples

The study protocol was approved by the ethics review board of Shandong University. We have obtained written informed consent from all study participants. All of the procedures were done in accordance with the Declaration of Helsinki and relevant policies in China. Because low molecular weight heparin anticoagulant therapy was invalid, all 12 females with CVST

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Table 1. Baseline characteristics of 12 patients

Case no.	Age (y)	Delivery	Gravidity history	ICP (mmH ₂ O)	Onset from postpartum	Mental status	GCS	Seizure	Hemiplegia	ICH or infarct	DSA
1	31	Cesarean section	G2P2	360	8d	comatose	11	Y	Y	ICH and infarct	SSS+SigS
2	21	Cesarean section	G1P1	360	15d	comatose	11	Y	Y	Infarct	SSS+TS+SigS
3	22	eutocia	G1P1	310	6d	Somnolence	13	Y	Y	ICH and infarct	SSS+TS
4	34	eutocia	G2P2	330	4d	Somnolence	13	N	Y	Infarct	SSS+TS+StrS+SigS
5	21	eutocia	G1P1	>400	9d	comatose	11	Y	Y	ICH and infarct	SSS
6	23	eutocia	G1P1	>400	15d	comatose	12	Y	N	ICH and infarct	SSS+TS
7	21	eutocia	G1P1	310	12d	comatose	11	N	Y	ICH and infarct	SSS
8	22	Cesarean section	G1P1	>400	10d	Mild coma	6	N	Y	ICH and infarct	SSS+StrS
9	34	Cesarean section	G3P3	350	16d	comatose	12	Y	Y	Infarct	SSS
10	25	eutocia	G1P1	380	8d	Mild coma	6	Y	Y	ICH and infarct	SSS+TS
11	22	eutocia	G1P1	330	11d	comatose	12	Y	Y	ICH and infarct	SSS+TS
12	28	Cesarean section	G1P1	>400	14d	Mild coma	6	Y	Y	ICH and infarct	SSS+TS

SSS, Superior sagittal sinus; TS, Transverse sinus; StrS, Straight sinus; SigS sigmoid sinus; ICH, intracranial hemorrhagic.

Table 2. Treatment characteristics of 12 patients

Case no.	Anticoagulant therapy (LMWH)	local thrombolytic therapy	The average amount of Urokinase	First month after local thrombolysis	Second-sixth Month after local thrombolysis
1	26 d	3 d	1,550,000 IU/d	Clopidogrel bisulfate + aspirin	Clopidogrel bisulfate
2	15 d	6 d	700,000 IU/d	Clopidogrel bisulfate + aspirin	Clopidogrel bisulfate
3	11 d	5 d	920,000 IU/d	Clopidogrel bisulfate + aspirin	aspirin
4	18 d	4 d	1,340,000 IU/d	Clopidogrel bisulfate + aspirin	Clopidogrel bisulfate
5	29 d	5 d	1,180,000 IU/d	Clopidogrel bisulfate + aspirin	Clopidogrel bisulfate
6	25 d	6 d	1,080,000 IU/d	Clopidogrel bisulfate + aspirin	Clopidogrel bisulfate
7	41 d	5 d	990,000 IU/d	Clopidogrel bisulfate + aspirin	aspirin
8	21 d	4 d	1,100,000 IU/d	Clopidogrel bisulfate + aspirin	Clopidogrel bisulfate
9	29 d	4 d	900,000 IU/d	Clopidogrel bisulfate + aspirin	aspirin
10	23 d	5 d	900,000 IU/d	Clopidogrel bisulfate + aspirin	aspirin
11	21 d	4 d	1,000,000 IU/d	Clopidogrel bisulfate + aspirin	Clopidogrel bisulfate
12	29 d	5 d	900,000 IU/d	Clopidogrel bisulfate + aspirin	Clopidogrel bisulfate

during postpartum from January 2008 to December 2013 were received local thrombolytic therapy by IST and mechanical thrombus maceration. The average age was 23.8 year-old (ranged from 21 to 34 year-old). The average time from postpartum to onset was 11 days (range from 4 to 16) (**Table 1**).

All patients were mainly with headache, consciousness, cranial nerve palsy, hemiplegia, epilepsy and mental disorder. Intracranial pressures were over 300 mmH₂O; optic disc edema; GCS score ranged from 6 to 13 (average 9.3). Preoperative CT, MRV, DSA were performed. And they were confirmed by DSA (**Table 1**).

Inclusion Criteria: 1) After anticoagulant therapy, disease still aggravated. 2) Coma.

Mechanical thrombus maceration

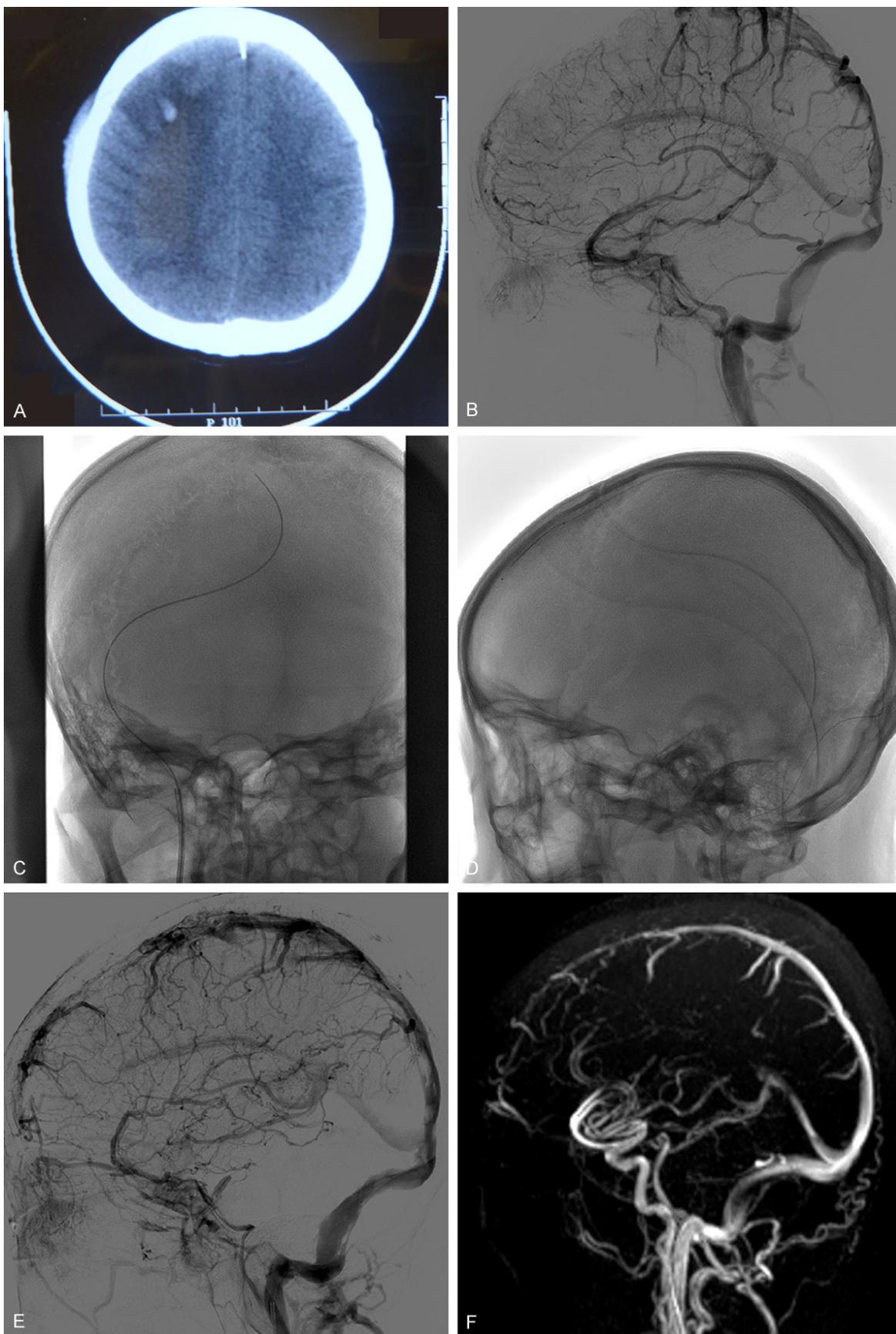
A 6 F guiding catheter started at the right femoral vein was inserted into the internal jugular

vein over the guide wire. Then the guide wire was advanced via transverse sinus and sigmoid sinus into the superior sagittal sinus. The guide wire was pulled in and out repeatedly to dissect the clot mechanically.

Intrasinus thrombolysis

A 3 F guiding catheter was inserted into superior sagittal sinus at distal thrombus over the guidewire. Then, the catheter was left (lasting about 4-6 d). And one million IU of urokinase (50,000 IU/min) was administered as a pulse therapy, then continuous urokinase (50,000-60,000 u/h) was infused into superior sagittal sinus through micro-catheter (**Table 2**). Coagulation function test was checked per 2-3 h. Prothrombin time was controlled at 18-30 s. International normalized ratio (INR) was controlled to be between 1.5 and 2.5. Fibrinogen was controlled to be over 1000 mg/L. DSA was performed every day. The catheter would be

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Figure 1. A: Cerebral CT at admission. B: Cerebral DSA before treatment. C: Mechanical thrombus maceration by guide wire. D: Microcatheter in the distal end of superior sagittal sinus. E: DSA after 5 days of local thrombolytic therapy. F: MRV after 6 months of anti-platelet aggregation treatment.

pulled out gradually, if all or most of thrombus was dissolved. Sinus recanalization was the main thrombolytic termination indicator.

During acute stage, all patients were received low molecular weight heparin anticoagulant therapy. After IST, they were all received anti-platelet aggregation (clopidogrel bisulfate and/or aspirin) for 6 months (**Table 2**). The follow up study was performed per half year for 6-70 months (average 37.4 months), including lumbar puncture, fundus examination, DSA or MRV.

Results

In all 12 cases, 9 patients were recanalized completely, 3 patients were part-recanalized with cortical veins and venous collateral circulation compensation. Except a case remained hemiparesis, 11 of them were recovered. Retinal edema was remarkably reduced or disappeared; intracranial pressure was reduced to below 200 mmH₂O; GCS score became 15. Urokinase associated intracranial or systemic bleeding were not found. The follow-up study indicated that no thrombosis and new neurological symptoms occurred.

Illustrative cases

In **Figure 1**, a 22 year-old female, was of headache, nausea, vomiting at postpartum 6th day. Before 7 h of admission, tonic-clonic seizures, obstructive consciousness, bilateral papilledema, positive bilateral pathologic reflex. Intracranial pressure was 310 mmH₂O. CT showed right frontal lobe infarction and hemorrhage. DSA showed CVST involving superior sagittal sinus and left transverse sinus. On the basis of low molecular weight heparin anticoagulant therapy (11 d), we performed IST and mechanical thrombus maceration. After 5 days, the patients became normal, and all pathological features disappeared. Intracranial pressure reduced to 150 mmH₂O. DSA showed that the superior sagittal sinus and transverse sinus were recanalized. The patient was asymptomatic at discharge. MRV showed complete recanalization of superior sagittal sinus and left transverse sinus after anti-platelet aggregation treatment for 6 months. In 46 months follow

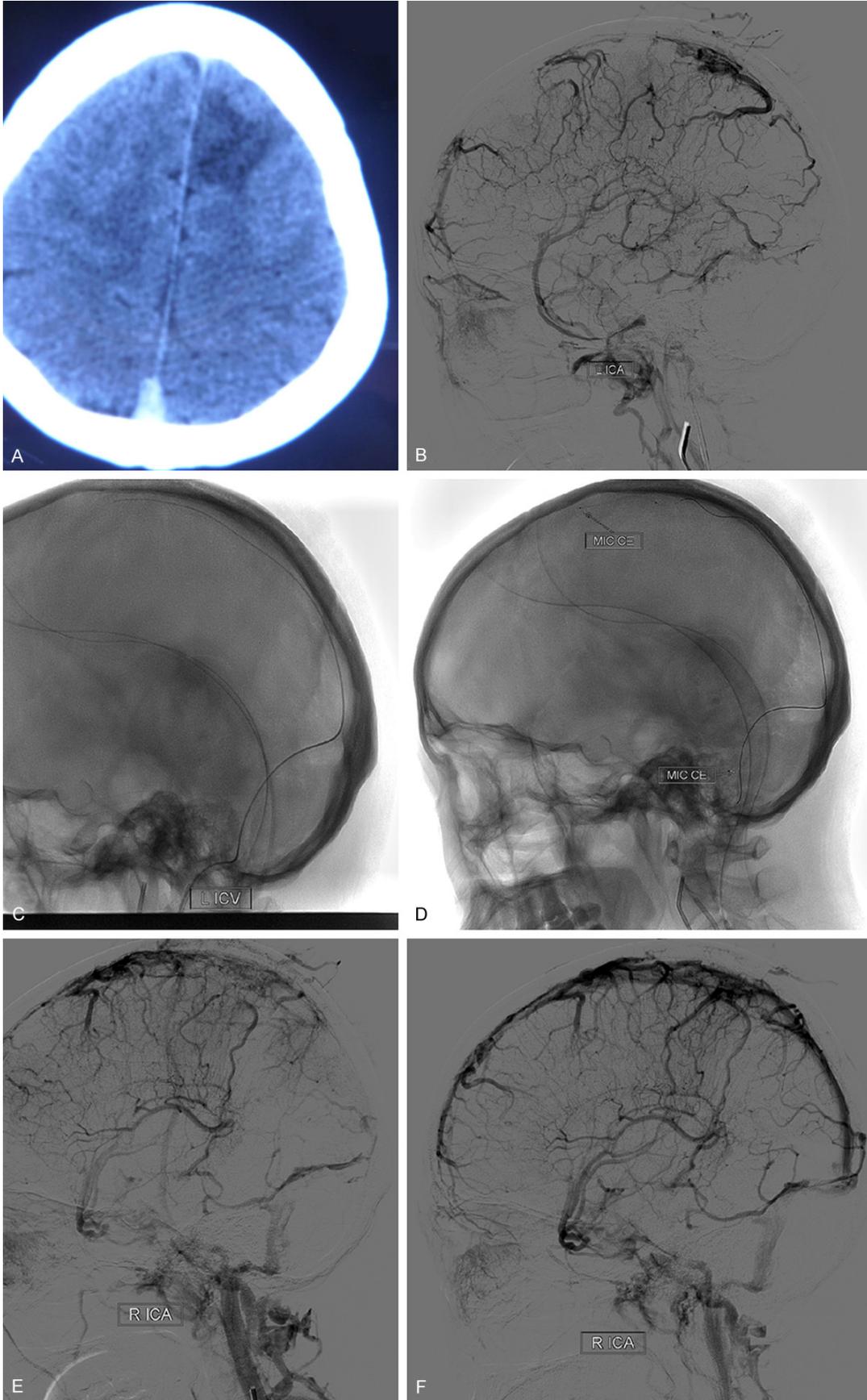
up, no thrombosis and new neurological symptoms occurred.

In **Figure 2**, a 34 year-old female, was of headache, nausea, vomiting and tonic-clonic seizures at postpartum 3rd day. Before admission, drowsiness, bilateral papilledema, right facial and lingual hemiplegia, right hemiplegia. Intracranial pressure was 330 mmH₂O. CT showed cerebral infarct and dense triangle sign in superior sagittal sinus. DSA showed thrombosis at superior sagittal sinus, inferior sagittal sinus, straight sinus, transverse sinus and sigmoid sinus. One million IU of urokinase (50,000 IU/min) was administered as a pulse therapy via micro-catheter, DSA showed that frontal-partial superior sagittal sinus, transverse sinus and sigmoid sinus were partially recanalized. On the basis of low molecular weight heparin anticoagulant therapy (18 d), we performed continuous urokinase thrombolysis (50,000-60,000 u/h) and mechanical thrombus maceration. After 4 days continuous urokinase treatment, DSA showed recanalization of superior sagittal sinus, transverse sinus and sigmoid sinus, whilst inferior sagittal sinus and straight sinus were still blocked. The patient became consciousness, and all pathological features disappeared. Intracranial pressure was reduced to 180 mmH₂O. After 18 days of discharge, facial and lingual hemiplegia were recovered. Anti-platelet aggregation treatment was performed for 6 months. The follow-up study for 29 months indicated that no thrombosis and new neurological symptoms occurred.

Discussion

Superior sagittal sinus is the main return channel of cerebral venous system. It is also the main recirculation pathway of cerebrospinal fluid and the potential recirculation of cerebral deep veins. Superior cerebral vein is always obliquely through sagittal sinus. The valve to prevent backflow of blood. However, when the blood pressure of venous sinus is higher than that of the venous, the function of prevention will be invalid, rendering blood reflux via Trolard's and Labbe's vein. So this is the anatomical basis of local IST in superior sagittal sinus. Further, the lumen of the superior sagittal sinus

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Figure 2. A: Cerebral CT at admission. B: Cerebral DSA before treatment. C: Mechanical thrombus maceration by guide wire. D: Microcatheter in the distal end of superior sagittal sinus. E: DSA after a pulse therapy of one million IU of urokinase. F: DSA after 4 days of local thrombolytic therapy.

is big enough that can be easily to opera, which is one of reasons why we choose it.

Catheter-administered thrombolytic agent is an effective tool of IST in superior sagittal sinus. The continuous infusion of low-dose urokinase can enhance drug concentration of local IST and improve recanalization further [6, 7]. Dissolved thrombus can be eliminated via vein collateral circulation or sinus venosus. In addition, during IST, catheter can be pulled out gradually until sinus venosus was recanalized.

In this study, except a case remained hemiparesis, 11 of them were recovered. The superior sagittal sinus of 9 cases were completely recanalized, accounting for 75%. And 3 cases were partially recanalized with cortical veins and deep vein compensatory, accounting for 25%. Specifically, for a case, her superior sagittal sinus, inferior sagittal sinus, straight sinus were completely blocked. Her superior sagittal sinus was recanalized by anticoagulant therapy and local IST, whilst inferior sagittal sinus and straight sinus were still blocked. But, no symptom appeared at the time of discharge. So, collateral veins compensation was the main factor to solve his clinical symptoms.

Mechanical thrombus maceration before IST can promote thrombolysis [8, 9]. It is able to increase the contact area between thrombus and urokinase, reducing the need of urokinase and thrombolysis time. But during the procedure, operation requires gently.

All 12 cases in this study were with blocked superior sagittal sinus. The reason why we did not choose arterial thrombolysis is that cerebral venous has a wide range of collateral circulation. Before physiological blood circulation of recanalization, thrombolytic drugs may recirculate via collateral pathways, leading to low drug concentration requirement in thrombus [10].

Anti-coagulant therapy and anti-platelet aggregation treatment also play important roles in the whole treatment. As for postpartum women, dehydration or blood loss gives rise to high blood viscosity. Moreover, due to physiological and pathological reasons, increased blood coagulation factor and reduced fibrinolytic activity will keep blood in a hypercoagulable state,

which is a crucial mechanism of CVST. So anti-coagulant and anti-platelet aggregation treatment enable blood components be far from aggregation and thrombosis.

For the recurrence of CVST, anticoagulant therapy is known as an effective way to prevent [1, 11]. We also found that anti-platelet aggregation might be a beneficial way to prevent CVST. In this study, we performed local IST for 4-6 days. After venous sinus became unobstructed and smooth, as well as cortex venous and deep venous recovered to normal, we discontinued urokinase and used clopidogrel bisulfate (75 mg) and aspirin (0.3) for 1 month. Then, only one of the two drugs was chosen to continue for 5 months. The longest follow up time was 70 months, and the average time was 37.4 months. No complication and thrombosis occurred. Therefore, as for recurrence of CVST, postoperative clopidogrel bisulfate and aspirin combined anti-platelet aggregation treatment is safe and effective.

In this study, continue urokinase via microcatheter was infused into superior sagittal sinus for 3-6 days (the maximum dose was 2,200,000 U/day, average dose was 700,000-1,550,000 U/days). And we found that the urokinase period was positively associated with urokinase dose. Prothrombin time, INR, fibrinogen were checked to adjust urokinase dose for preventing cerebral bleeding complications.

In conclusion, local IST is safe and effective for patients with severe CVST during puerperium. Collateral circulation compensation plays a significant role in convalescence. And clopidogrel bisulfate and aspirin combined anti-platelet aggregation treatment is also safe and effective for preventing recurrence of CVST. Anti-platelet aggregation may be considered as a valid alternative treatment for preventing recurrence of CVST during puerperium. Our results suggest that anti-platelet aggregation therapy is an effective way to prevent CVST and recurrence during puerperium.

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Disclosure of conflict of interest

None.

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