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Is it dangerous to treat spontaneous intracerebral hemorrhage by minimally invasive surgery plus local thrombolysis in patients with coexisting unruptured intracranial aneurysms?

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ABSTRACT

Objectives: Limited evidence supports the presumed increased frequency of hemorrhage caused by the unruptured intracranial aneurysms which coexist in patients with spontaneous intracerebral hemorrhage treated with minimally invasive surgery plus local thrombolysis. Subsequently, we sought to determine the safety of local thrombolysis for this particular subset of patients.
Patients and Methods: We reviewed the medical records of patients treated with minimally invasive surgery plus local thrombolysis for intracerebral hemorrhage between November 2013 to December 2015 in an intensive care unit of a tertiary care hospital. Depending upon the vascular images, unruptured intracranial aneurysms were identified. The primary outcome was any of postoperative intracranial rebleeding. The second outcome included the 30-day death and 6-month follow up graded by Modified Rank Scale. Blind abstractors reviewed the medical data and binary logistic regression was performed to investigate the risk factors of poor prognosis.
Results: We identified a cohort of consecutive 188 patients, of whom 23 (12.2%) harbored unruptured intracranial aneurysms. There were 28 aneurysms documented in this study, among which 3 were in the posterior circulation. And in total, 20 (11.3%) cases suffered from postoperative hematoma growth, of which 4 were with aneurysms. Additionally,the 30-day mortality after stroke in patients with aneurysms was 8.69% (2/23), comparable to 13.33% in without (22/165,p = 0.744). The proportion of the favorable outcome at 6-month follow-up in patients with aneurysms was comparable to that in without (47.8% versus 48.5%,p = 1.000) Insignificant associations were demonstrated between the unruptured intracranial aneurysms and postoperative intracranial rehemorrhage (p = 0.092), 30-day death(p = 0.588) and poor long-term prognosis (p = 0.332), respectively.
Conclusion: Our findings suggest that unruptured intracranial aneurysms seem to represent no increased risks of poor outcome after local thrombolysis for intracerbral hematomas.

1. Introduction

Spontaneous intracerebral hemorrhage (ICH) leads to high mortality, morbidity and disability throughout the world [1],especially in China [2] where there are more than 100,000 deaths and approximately 300,000 disabilities every year.

The intracerebral clot burden is one of the most powerful indicators affecting the prognosis of patients with ICH [1]. However, with the termination of previous randomized trials [3,4] comparing surgery with conservative management, there is a strong indication that open craniotomy for hematoma evacuation does not produce the presumed benefits. By contrast, recent emerging studies have shown patients with ICH can benefit from favoring accelerated clot reduction and positive modification for functional outcome by the technique of minimally invasive surgery (MIS) plus local thrombolysis, which displays the robust potential as a unique intervention for ICH [5–8].

However, mounting pragmatic data including our previous findings [9–11] shows MIS plus local thrombolysis cannot be combined without the occurrence of postoperative hemorrhage which may negatively affect the outcome of ICH victims. Subsequently, this complication should

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be managed with clinical vigilance.

At the same time, it's also reported the unruptured intracranial aneurysms (UIAs) in ICH patients are not uncommon with the incidence of approximately 8–14%, which is higher than the normal crowd (2.3–6%) [12,13]. In theory, the coexisting UIAs are potential risk factors leading to vessel rupture and bleeding in ICH patients, especially for those treated with local thrombolytic therapy. Subsequently, this concern may affect the frequency of local thrombolysis for patients with ICH and coexisting UIAs in clinical practice. Anyway, in addition to the clot lysis per se, recombinant tissue plasminogen activator(rtPA), a kind of agent for thrombolysis, still implies potential neurotoxity by damaging the blood brain barrier and inducing cerebral hemorrhage [14,15]. Indeed, some patients developed subarachnonid hemorrhage (SAH) with symptom deterioration after the administration of rtPA for the ischemic stroke [16] in the presence of UIAs. However, there is still minimal data regarding the effect of co-morbid UIAs on the outcome of ICH patients treated with local thrombolysis.

Given this, we aimed to present our experience about the intracrainial hemorrhagic complications following the MIS plus rtPA for the ICH patients and determine the safety of local thrombolysis for patients with ICH and coexisting UIAs through a retrospective cohort study.

2. Patients and methods

2.1. Compliance with ethical standards

This study was approved by the ethics committee of Tongji hospital, Tongji medical college, Huazhong University of Science and Technology. The whole clinical research was conducted following the principles of Declaration of Helsinki. Written informed consent was obtained from each patient or his closest relative.

2.2. Patients and subjects

We retrospectively reviewed the medical and neuroimaging records of the patients treated with MIS plus rtPA infusion between November 2013 and December 2015 in our division. All the subjects were diagnosed as ICH by the non-contrast CT scan.Eligibility criteria for the MIS consisted of: supratentorial hematoma without brain stem function failure, hematoma volume ≥20 ml, Glasgow Coma Scale (GCS) score ≥5 at admission, no structural etiology to account for the hemorrhage, no traumatic intracranial hematoma, no recent craniotomy or surgery (< 30 days), no systemic bleeding diathesis and no severe concurrent illness affecting heart, liver, lung or kidney. The cerebral angiography (3D-CT angiography) was performed for every case before MIS to rule out the abnormal vascular structure as the bleeding origin. The UIA was determined by consensus among the treating neurosurgeon,neurologist and neuroradiologist based on the clinical evidence (e.g. paralysis without isolated cranial nerve palsy) and radiographic evidence (e.g. lack of subarachnoid hemorrhage(SAH), location of the clot and aneurysm in different arterial territories).But the neurosurgeons did not have any data in relation to whether unruptured intracranial aneurysms were detected on the preliminary radiology reads before the operation. And the individuals who analyzed the radiological data and performed the follow-up assessment had no idea about the whole study protocol. The cases with UIAs were listed in UIA group and those without UIAs were in control group.

2.3. Medical management

Medical therapy was administered under the current guidelines including: general monitoring and nursing care, moderate blood pressure intervention, deep vein thrombosis prophylaxis, appropriate nutritional support, medical complications management and so on [1]. Patients with dyspnea would be given endotracheal intubation or with mechanical ventilation. Rountine blood test and biochemical indexes as well as coagulation function was rechecked at regular intervals.

2.4. Operation and imaging monitoring protocol

All the operations were performed at bedside under local anesthesia with or without intravenous sedation in the neurology intensive care unit of our division. With the guidance of Leksell stereotactic frame (Elekta, AB,Stockholm,Sweden), the YL-1 puncture needle (designed for broth puncture and drainage by Wantefu Company, Beijing, China) was inserted into the core of the clot through a burr hole after local disinfection. The introducer portion of the cannula was then removed and a three-way stopcock with closed drainage was connected to the catheter. Postoperative CT were performed to confirm positioning of the catheter and stability of the residual haematoma and catheter tract. The rtPA at 0.3 mg–1 mg in 1 ml saline was injected into the clot though the catheter and the drainage system was closed for 2 h to achieve dose-clot reaction.The CT scan and rtPA infusion was repeated everyday until the clot around the tip of the needle seemed nearly invisible or the needle fenestrations were no longer in continuity with the clot. Subsequently the needle and catheter were removed [11].

2.5. Outcome evaluation

The primary outcome of these ICH victims was identified by whether there was any intracranial rehemorrhage following the MIS plus the local administration of rtPA as well as various subtypes of the intracranial rebleeding including symptomatic ICH. The symptomatic ICH is defined as an increase in clot volume (> 5 ml) associated with a decrease in the GCS score of more than 2 points sustained for a minimum of 8 h or associated clinical symptoms in the opinion of the clinical investigator [6]; In addition, according to the bleeding location, subtypes of the intracranial rehemorrhage also included rebleeding in SAH,epidural, along the puncture trajectory and original clot site. Further, based on the bleeding time, subtypes of the intracranial rehemorrhage still consisted of rebleeding after puncture,thrombolysis or drainage and catheter removal. The second outcome included the 30-day fatality and 6-month outcome. The long-term prognosis was assessed by the modified Rankin Scale(mRS) and it was considered as a poor outcome when mRS score was of > 3 [17] at 6-month follow up. The blind abstractors performed the long-term outcome evaluation by phone and they did not involved in the patients' treatment.

2.6. Statistical analysis

Normally distributed continuous variables were reported as mean ± standard deviation and non-normally distributed variables as median (25th-75th percentage). Categorical variables were presented as frequency (percentage). Independent-samples *t* test (for parametric data) or the Mann-Whitney *U* test (for non-parametric data) compared the distributions of continuous variables between groups. A 2-sided Fisher exact-test was applied to compare the proportions between the groups. Binary logistic regression analysis was used to assess the risk of postoperative rebleeding, 30-day death and poor long-term outcome respectively. All factors were initially entered as covariates in the enter model. The difference was considered significant if $p < 0.05$. All statistical analyses were performed by an SPSS software pack-age (Version 22.0; IBM Corporation, Armonk, NY).

3. Results

A cohort of consecutive 188 cases were included in this study. The average age of the patients was (54.41 ± 10.76) years, 123 of them were male. Among these patients, there were 133(70.74%) cases with a history of hypertension,10(5.3%) with diabetes and 49(26.06%) with smoking. The clot lied on the left in 89 cases. The interval between ICH

Table 1
The demographic and clinical data of the ICH patients with coexisting UIAs.

patient No.	Volume of hematoma (ml)	Clot location	Aneurysm type	Aneurysm location	Size of Aneurysm (mm)	Rehemorrhage (location, time point)
1	36	R,Basal ganglia	saccular	MCA (L)	2.4	no
2	35	L,Basal ganglia	saccular	ICA(L)	3.5	no
3	76	R,Temporal lobe	saccular	A.comm	2.9	no
4	60	R,Basal ganglia	Multiple			no
			Saccular	A.comm	2.4	
			Fusiform	MCA(L)	5.1	
5	33	L,Basal ganglia	saccular	ICA(L)	2	no
6	35	R,Basal ganglia	saccular	MCA(L)	7.3	no
7	22	R, thalamus	saccular	ICA(R)	2.5	Yes(original clot site, after rtPA infusion)
8	27	R,Temporal lobe	saccular	ICA(L)	1.8	no
9	32	L,Basal ganglia	saccular	ICA(L)	2.0	no
10	24	R, thalamus	saccular	ICA(R)	2.5	Yes(SAH,after catheter insertion)
11	75	L,Basal ganglia	Multiple			no
			Saccular	ICA(L)	1.2	
			Saccular	ICA(R)	2.0	
12	40	R,Temporal and parietal lobe	Multiple			no
			Saccular	ACA(L)	2.5	
			Saccular	ICA(R)	2.5	
13	38	R,Temporal and parietal lobe	Multiple			Yes(epidural,after catheter insertion)
			Saccular	ICA(R)	1.7	
			Saccular	A.comm,	1.7	
14	27	R,Basal ganglia	Saccular	ICA(R)	1.9	no
15	49	R,Basal ganglia	Fusiform	ICA(R)	1.7	no
16	87	R,parietal lobe	Saccular	ICA(L)	3	no
17	64	L,Basal ganglia	Multiple			no
			Saccular	P.comm(L)	0.5	
			Fusiform	PCA(L)	0.5	
18	44	R,Temporal and parietal lobe	Saccula	A.comm	5	no
19	53	R,Basal ganglia	Saccular	ICA(R)	3.7	no
20	44	R,Basal ganglia	Saccular	ICA(L)	1.7	no
21	58	L,Basal ganglia	Saccular	PCA(R)	1.5	no
22	84	R,Basal ganglia	Saccular	Basilar A.	5.8	no
23	40	R,Basal ganglia	Saccular	A.comm	1.5	Yes(original clot site, after rtPA infusion)

ICH indicates Spontaneous intracerebral hemorrhage; UIAs, unruptured intracranial aneurysms; SAH, subarachnonid hemorrhage;rtPA, recombinant tissue plasminogen activator; GCSs, Glasgow Coma Scale score; M: male; R, right; MCA, middle cerebral artery; L, left; ICA, internal carotid artery; A.comm,anterior communicating artery; F, female; ACA, anterior cerebral artery; P.comm, posterior communicating artery; Basilar A, basilar artery.

and the operation was 56.50(37.25–96.2)h. Single-target puncture was performed in 152 patients and multiple-target in 36 cases.

Due to the poor life condition or the withdraw of active care by the closest relatives' will, 11 patients in control group failed to undergo the brain CT recheck after the complete drainage and catheter removal, leading to the deficiency in the data respecting the results of post-operative incranial rebleeding.

The co-existence of UIAs were detected in 23(12.2%,95%CI: 7.5%–16.9%) cases in all preceding the surgery, whose demographic and clinical characteristics was presented in Table 1. There were 28 aneurysms all together in the 23 patients with UIAs, of whom 5 cases harbored multiple aneurysms. A small minority of these aneurysms (3/28, 10.7%) were revealed in the posterior circulation. The majority of the aneurysms (25/28, 89.2%) were smaller than 5 mm in diameter.

The perioperative changes about the clinical manifestation of the patients with UIAs and without were described in Table 2. The patients with UIAs displayed either no significant difference compared with control about the clinical characteristics involved in the surgery, including the interval between symptom onset and catheter insertion (48(24–80) versus 60(44–96)h, p = 0.189), the ratio of single puncture (17/23,73.9% versus 135/165,81.8%, p = 0.397) and the duration of drainage (6.5(5–7) versus 6(4–7)d, p = 0.161). In addition,the mean dosage of rtPA for those individuals with coexisting UIAs was also similar to that of control(1.0(0.5–1.5) versus 0.9 (0.4–1.0)mg, p = 0.275).

Patients with any as wells as various subtypes of the postoperative intracranial rebleeding, including SAH, between UIA group and control

Table 2
The baseline demographic and clinical data between groups.

group	UIAs (n = 23)	Control (n = 165)	P
Gender(Male/Female)	18/5	/105/60	0.242
Age(years)	55.96 ± 9.90	54.23 ± 10.89	0.446
diabetes(yes/no)	122	9/156	1.000
Hypertension(yes/no)	18/5	115/50	0.471
Cardiovascular disease(yes/no)	221	18/147	1.000
smoking(yes/no)	7/16	42/123	1.000
Alcohol abuse(yes/no)	3/20	31/134	0.772
SBP(mmhg)	154.86 ± 19.76	162.39 ± 21.46	0.101
DBP(mmhg)	89.70 ± 14.37	93.27 ± 16.96	0.282
Fibre protein(g/L,IQR)	3.24(2.65-3.91)	3.45(2.99-3.98)	0.234
PLT	190.82 ± 64.80	192.47 ± 57.75	0.900
Hematoma location(deep/lobar)	17/6	140/25	0.227
Side(left/right)	7/16	82/83	0.118
Hematoma size (ml,IQR)	40.00(33.32-60.42)	37.33(29.31-54.39)	0.216
MLS (mm)	7.97 ± 3.44	7.49 ± 3.62	0.549
GCSs (IQR)	10(7-13)	9(7-10)	0.089

UIAs:the group with unruptured intracranial aneurysms; Control: the group without unruptured intracranial aneurysms; SBP: systolic blood pressure; DBP: diastolic blood pressure; IQR:interquartile range; MLS: midline shift; GCSs, Glasgow Coma Scale score.

Table 3
Summary of various postoperative intracranial rehemorrhage.

Group	UIAs (n = 23)	Control (n = 154)	P
Any rehemorrahge (yes/no)	4/19	16/138	0.301
Sympotmatic rebleeding (yes/no)	2/21	6/148	0.278
Rebleeding in subarachnoid (yes/no)	1/22	5/149	0.572
Rebleeding in epidural (yes/no)	1/22	2/152	0.343
Rebleeding along puncture trajectory (yes/no)	0/23	2/152	1.000
Rebleeding in original clot site (yes/no)	2/21	11/143	0.678
Rebleeding after puncture (yes/no)	2/21	7/147	0.331
Rebleeding after thrombolysis and drainage (yes/no)	2/21	7/147	0.331
Rebleeding after catheter removal (yes/no)	0/23	4/150	1.000

UIAs:the group with unruptured intracranial aneurysms; Control: the group without unruptured intracranial aneurysms.

Table 4
The outcome t of 6-month follow-up between groups.

	UIAs (n = 23)	Control (n = 165)
mRS = 0(n,%)	0	0
mRS = 1(n,%)	4(17.39%)	23(13.93%)
mRS = 2(n,%)	4(17.39%)	22(13.33%)
mRS = 3(n,%)	3(13.04%)	35(21.21%)
mRS = 4(n,%)	8(34.78%)	32(19.39%)
mRS = 5(n,%)	0	9(5.45%)
mRS = 6(n,%)	3(13.04%)	35(21.21%)
MRS Missing	1(4.34%)	9(5.45%)

UIAs:the group with unruptured intracranial aneurysms; Control: the group without unruptured intracranial aneurysms; mRS: modified rank scale score.

were described in Table 3.The proportion of any as wells as various subtypes of the postoperative intracranial rebleeding, including SAH,in groups were noted in Table 4. The frequency of postoperative hematoma growth was 20/177(11.3%) of all the subjects (Fig. 1). Subsequently,two of them crossed over to the traditional open craniotomy No significant difference was found between groups regarding to the proportion of any as wells as various subtypes of the postoperative intracranial rebleeding.

The 30-day death was confirmed in 24 cases(14/130,10.77%), including 2 in the UIA group and 22 in control. Eight of them died of the postoperative rebleeding and 11of the remaining patients suffered from the irreversible serious pneumonia. The death of the other 5 patients was attributed to the withdrawl of medical support. Two groups showed the similar 30-day mortality (8.69%,2/23 vs 13.33%,22/165,P = 0.744)

The description for the long-term outcome assessment was shown in the Table 4. At the 6-month follow-up, we failed to get in touch with 10 cases in total, including 1 in the patients with UIAs and 9 in without. About 47.8% achieved good outcome in patients with UIAs, similar to that in without (48.5%,p = 1.000).

The statistically significant risk factors of postoperative intracranial rebleeding, 30-day death and poor outcome at 6 month were listed in Table 5. The coexistence of UIAs failed to show significant association with the postoperative intracranial rebleeding (p = 0.092), 30-day death(p = 0.588) or the poor outcome at 6 month follow up (p = 0.332), respectively.

4. Discussion

This study further verified that it was not uncommon that UIAs, a potential risk for intracranial hemorrhage or poor prognosis, coexisted in patients with ICH. And patients with pre-existing UIAs accounted for about 12% among a total of 188 consecutive ICH cases in this study, consistent with the results reported by K. Matsumoto et al [13]. Therefore, it is not a trifle about the surgical management relating to the ICH patients who harbored UIAs because the aneurysm usually is a weakened and bulging area in the cerebral wall, rupturing easily whether under natural conditions or during thrombolysis [18]. Though extensive data [18,24] has repeatedly demonstrated the safety regarding intravenous rtPA thrombolysis for acute ischemic stroke patients harboring UIA, it is still unclear whether the different dose and administration method of rtPA is safe for a different pathology(ICH with UIAs). On the other hand, the rapid clot evacuation is helpful to improve the prognosis for patients with ICH. Hence, the possibility of UIAs to induce intracerebral hemorrahge and worsen the outcome of ICH patients often makes it difficult for neurosurgeons to decide whether to perform the MIS plus local thrombolysis for this special subpopulation in clinical practice. However, thefindings in this study failed to demonstrate significant association between the UIAs and postoperative intracranial rehemorrhage, 30-day death and poor long-term prognosis, respectively. These results seem to suggested that UIAs didn't produce the presumed increased risks of intracerebral bleeding or negatively modified outcome following the MIS plus rtPA.

There is possibly several casual factors listed below to support the above view: (1)Most of the UIAs in this study were small in size (diameter < 5 mm), and the risk of rupture of these aneurysms is relatively lower [18,19]. (2) The target point of the catheter placement during the procedure of MIS and local rtPA infiltration was limited in the hematoma cavity, relatively far away from the UIAs; (3) when other confounding factors were ruled out including blood prssure [20], abnormal coagulation function [21] and criminal vascular abnormalities [22], there may be a closer relationship between the postoperative intracerebral rebleeding and the surgery procedures such as the local infusion of liquefaction agents, the insertion and removal of the catheter. This may be attributed to that in this study, the postoperative hematoma growth was mainly restricted in the areas(e.g epidural and original clot site) where surgery procedures may affect directly, instead of the subarachnoid where the rupture of aneurysms was more likely to occur.

It is should be interpreted about the weakness of the current study in the following. (1) Given the low incidence rate of UIAs and single-centre nature in design, our investigation was limited by a small sample size. This means the collection of data was potentially biased. However, the results of this research should be of important clinical guidance since the report is rare on the association between the coexisting UIAs and the outcome of ICH patients treated with local thrombolysis. Anyway, larger clinical trials are deserved to provide more powerful evidence. (2) Clinically, aneurysms still contribute to a possible risk for vessels rupture and bleeding, leading to the current tendency that a more conservative treatment would be chosen other than the local thrombolysis for the management of ICH once the existence of UIAs is conformed. Thus, the level of evidence about our observation is limited to a retrospective study. (3) Majority of the UIAs in this study were of small diameter and we failed to include the ICH patients with large UIAs into this cohort, creating a potential source of choice bias in this study. But on the other hand, it's reported by the previous literature that approximately 92% of patients with UIAs have aneurysms < 10 mm in size. Thus, the size of aneurysms in our study is consistent with the characteristic of unruptured aneurysms in general [23,24].

In conclusion, our findings suggest that coexisting UIAs do not seem to increase the likelihood of intracerebral rebleeding or poor outcome of patients with ICH treated with local thrombolysis. This implies that the UIAs should not be listed as a contradiction for MIS plus local thrombolysis.

Conflicts of interest

The authors report no conflict of interest concerning the materials

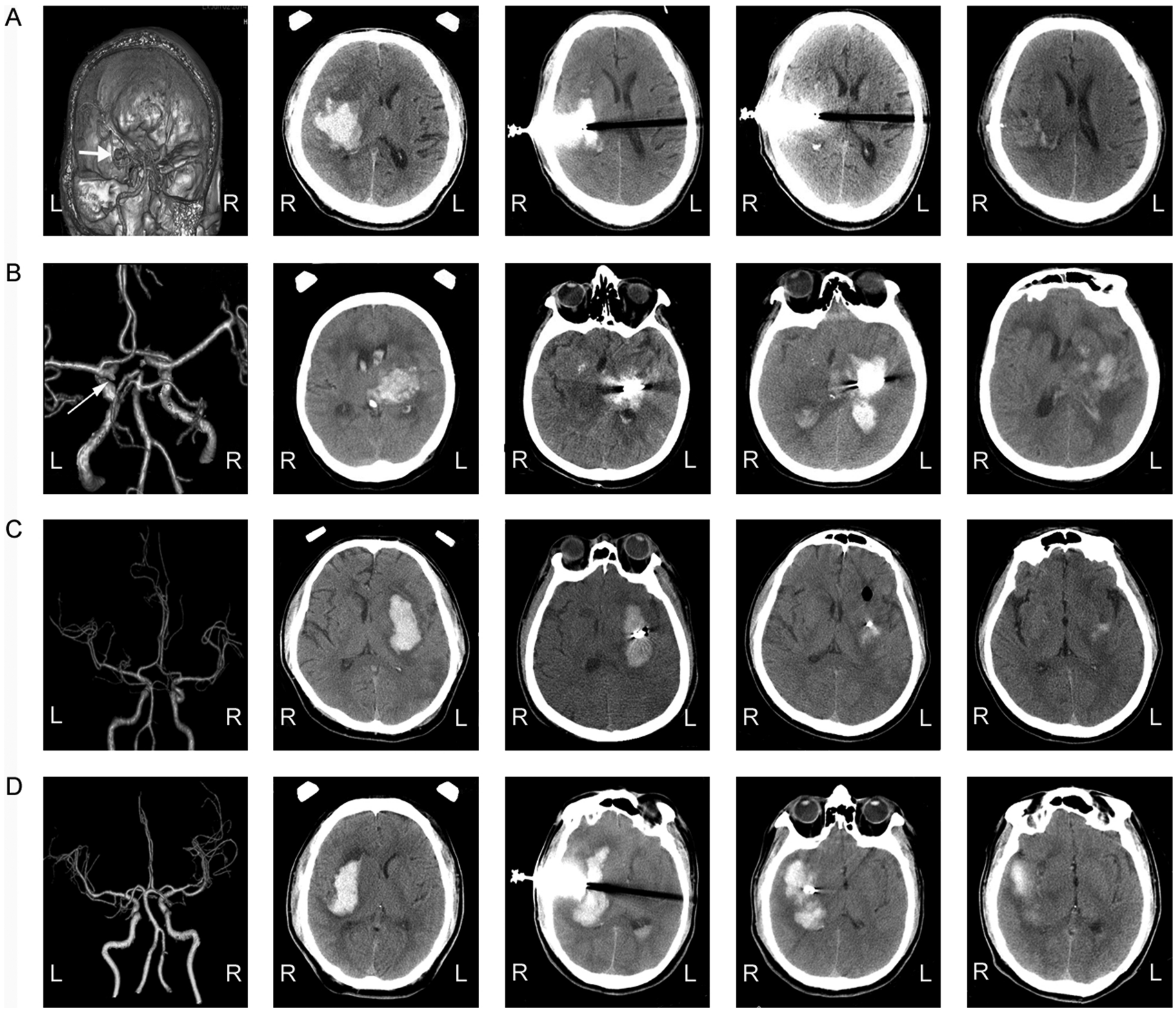

Fig. 1. CT angiography (CTA) of intracerebral hemorrhage(ICH) patients before the surgery (left) and CT non-contrast scans after the fixation of leksell coordinate frame(middle left) on the head, after catheter placement (before thrombolysis, middle), after the first recombinant tissue plasminogen activator(rtPA) infusion and drainage (after thrombolysis, middle right) as well as after the removal of the catheter (right). (A) represents a patient haboring a hematoma on the right basal ganglia with an unruptured intracranial aneuyrsm(UIA) (white arrow) on the trifurcation of the left middle cerebral artery but without postoperative rebleeding ; (B) displays a patient who suffered from a supratentorial hemorrhage on the left as well as the postoperative rebleeding with an UIA (white arrow) at the C7 segment of the ipsilateral internal carotid artery; (C) shows an ICH patient with normal image findings of CTA but without postoperative rebleeding; and (D) presents an ICH patient with both normal image findings of CTA and postoperative rehemorrhage.R means right; L, left.

Table 5
Statistically significant risk factors (including UIAs) and associate effect of the outcome.

		P	OR	95% confident interval
Postoperative rebleeding	UIAs	*0.092*	0.29	0.069-1.224
30-day death	GCSs	< 0.01	0.583	0.435-0.779
	UIAs	*0.588*	0.6	0.094-3.808
poor outcome at 6-month follow up	age	0.03	1.063	1.021-1.107
	GCSs	0.001	0.752	0.638-0.886
	UIAs	*0.332*	0.571	0.184-1.770

UIAs: unruptured incranial aneurysms; GCSs: glasgow coma scale score.

or methods used in this study or the findings specified in this paper.

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