PREDICTION OF FUNCTIONAL OUTCOMES IN SUPRATENTORIAL INTRACEREBRAL HEMORRHAGE PATIENTS TREATED WITH STEREOTACTIC COMPUTED TOMOGRAPHIC-GUIDED ASPIRATION AND RECOMBINANT TISSUE PLASMINOGEN ACTIVATOR

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Abstract

Objectives: To evaluate factors influencing the outcomes in supratentorial intracerebral hemorrhage (ICH) patients treated with stereotactic computed tomographic (CT) guided aspiration and recombinant tissue plasminogen activator (rt-PA). ***Methods:*** A prospective study on 80 spontaneous supratentorial ICH cases from February 2017 to June 2020, analyzing the 12-month outcomes and identifying clinical and radiological factors for poor prognosis within 12 months. ***Results:*** The mean age was 55.6 years (SD 11.4). The median pre-operation GCS score was 9 (IQR 6 - 12). The mean final ICH volume was 23.9mL (SD 24.6), with ICH volume reduction by an average of 66%. 12 months after the procedure, 40 patients (50%) had poor outcomes (mRS score 4 - 6). In multivariate analysis, age (OR = 1.058, 95%CI = 1.007 - 1.112; p = 0.026), the GCS score before operation (OR = 0.666, 95%CI = 0.448 - 0.992; p = 0.046), the midline shift before operation (OR = 1.301, 95%CI = 1.057 - 1.601; p = 0.013), and the residual volume hematoma ≥ 20mL (OR = 4.402, 95%CI = 1.393 - 13.913, p = 0.012) were the significant predictors of a poor 12-month outcome. ***Conclusion:*** CT-guided thrombolysis and aspiration can be safe and effective in reducing ICH volume. Age, the GCS score before the operation, the midline shift before the operation, and final residual volume hematoma ≥ 20mL were significant predictors of a poor 12-month outcome.

Keywords: Intracerebral hemorrhage; Stereotactic aspiration; Recombinant tissue plasminogen activator (rt-PA); 12-month outcome; Prognosis.

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INTRODUCTION

Intracerebral hemorrhage, the second most frequent cause of stroke, is associated with a significant mortality and morbidity rate. Anticoagulation, amyloid angiopathy, and hypertension are risk factors for ICH, in which hypertension affects most ICH patients. The 30-day mortality rate approaches 40% in these patients; most survivors live dependently [1, 2]. Unfortunately, there has been no beneficial medical treatment for ICH, and the surgical hematoma evacuation for supratentorial ICH remains controversial. Attempts to remove hematoma via open surgery have failed to provide an effective alternative treatment for most ICH patients because they may cause damage to normal brain tissue, especially for individuals with profound hemorrhage. Therefore, minimally invasive surgery (MIS) is a promising surgical strategy for patients with ICH because of the shorter operation time, alleviation of the injury to the normal brain tissue, and ability to treat bedside. Moreover, the administration of rt-PA using MIS in ICH treatment has accelerated clot thrombolysis and has been reported to be safe by several studies [3, 4, 5]. In this research, we present our experience with consecutive cases of supratentorial ICH treated by stereotactic CT-guided aspiration and thrombolysis with alteplase. Our primary aim was: *To Investigate the technique's effectiveness, including procedure-related complications, clinical outcomes, and radiological results, as well as the factors related to patients' outcomes.*

MATERIALS AND METHODS

1. Subjects

80 patients were treated and evaluated at the Department of Neurosurgery, 108 Military Central Hospital , from February 2017 to June 2020.

* *Inclusion criteria:* Patients ≥ 18 years with spontaneous, non-traumatic, supratentorial ICH of 30mL or more, with a GSC score > 5 at admission; patients had no signs of transtentorial herniation; patients had no severe concurrent illness with life expectancy less than 12 months.

* *Exclusion criteria:* Patients with underlying structural etiology responsible for the hemorrhage, or systemic bleeding diathesis (abnormal prothrombin, partial thromboplastin times, or platelet count 100,000).

The patient charts were reviewed retrospectively, and the following variables were recorded: Age, sex, GSC score before surgery, the size,

location, and volume of the hematoma, the presence of a midline shift, intraventricular hemorrhage (IVH), and complications after MIS. The patient's outcome was assessed using the modified Rankin Scale (mRS) score at discharge and twelve months after ictus. We classified mRS scores into favorable (good recovery and moderate disability, mRS 0 - 3) or poor (severe disability, vegetative state, or death, mRS 4 - 6) outcomes.

2. Methods

* *Research method:* A prospective study was conducted.

* *Calculation of the hematoma volume:*

ICH volumes were calculated using the ABC/2 formula, in which A and B were the perpendicular maximal diameters of the lesion, and C was the total length in the vertical plane, using CTs obtained just before operation [6].

* *Operative technique, thrombolysis, and aspiration protocol:*

Following a preliminary assessment, eligible patients underwent a repeat CT-scan with a stereotactic protocol that used 0.5cm slices thick that were then loaded onto a Stealth Station S7 (Medtronic, Minneapolis, MN). With the stereotactic guidance software, the trajectory was aligned with the long axis of the clot. An ipsilateral frontal standard burr hole location (3cm lateral to the midline and just anterior to the coronal suture) was used for basal ganglia hemorrhage. In contrast, the burr hole was localized over the hematoma if the hematoma was lobar. Under general anesthesia in the operating room, a rigid cannula was inserted into the hematoma, and then one soft drainage catheter was passed into the hematoma's center under stereotactic guidance. Gentle aspiration was performed and stopped at the first sign of resistance. The catheter was then tunneled away from the incision, attached to a three-way stopcock, and left open, draining into a collection system. A post-operative or intraoperative CT was performed to confirm the placement of the catheter, and it was adjusted under CT guidance as necessary.

All patients were managed in a stroke intensive care unit; subsequent thrombolysis and clot aspiration were performed at the bedside using a sterile technique. Alteplase 1mg in 1mL was administered through the catheter and then flushed the catheter with 3mL of saline, followed by 1 hour of drainage closure. After 8 hours, manual aspiration of the lysed clot was attempted at the

bedside. The aspirated volume was recorded. Serial CT-scan were performed to assess the residual ICH volume. The administration of alteplase was stopped until the ICH volume diminished to 20mL or after a maximum of 7 doses. Under sterile conditions, the catheter was withdrawn from the patient at the bedside, and its exit site was closed off with an occlusive dressing after a single suture was placed. After the catheter was removed, a head CT-scan was performed to determine the size of the residual hematoma. Throughout treatment, all patients underwent close neurological monitoring and followed the current recommendations formulated by the American Stroke Association [7].

** Follow-up and outcome assessment:*

Post-operative neurological information was assessed by GCS score at the time of discharge and by mRS at 3, 6, and 12 months after the procedure. Follow-up examinations were performed by either the neurosurgery member or a stroke practitioner at the hospital or via video calls.

** Statistical analysis:*

Data were analyzed using the SPSS version 26.0 software program (SPSS, Chicago, IL, USA). The mean reduction in hematoma volume was calculated and recorded. First, univariate logistic regression was used to assess the strength of the association between the collected variables and the 12-month outcome, using the poor 12-month outcome as a dependent variable. Independent variables included age, gender, GSC score, arterial hypertension, the volume of hematoma, hemorrhage location, presence of IVH, and the midline shift. In the next step, multivariate analysis was performed, using the poor 12-month outcome as a dependent variable and incorporating independent variables showing significance or a trend towards significance in the univariate analysis. Finally, to assess the goodness of fit of the multivariate model, we used a Hosmer-Lemeshow test. Results were reported as odds ratios (OR) and 95% confidence intervals (CI).

3. Ethics

Operative technique, thrombolysis, and aspiration protocol were approved by the Scientific Council of 108 Military Central Hospital according to decision No. 707/QD-BV dated March 16, 2017 of the Hospital Director.

All patients' data were secure throughout the study to protect the anonymity of the patients. All patients gave their family members written and informed consent to enter the study.

RESULTS

80 ICH patients were treated with stereotactic CT-guided aspiration combined with thrombolysis of intracerebral hematoma from February 2017 to June 2020. Details of all patients' age, gender, previous medical history, time in hours from stroke onset to operation, conscious disturbance before the procedure, stroke severity, and the neurological image are shown in table 1.

Table 1. Characteristics of 80 patients with intracerebral hemorrhage.

Age (years), mean	55.6 years (SD 11.4)	
Male (n, %)	64 (80%)	
Clinical history		
Stroke	6 (7.5%)	
Hypertension	63 (78.7%)	
Diabetes mellitus	14 (17.5%)	
Chronic alcoholism	26 (32.5%)	
GCS score on admission	10 (IQR 6 - 14)	
≤ 8	27	33.7%
9 - 12	44	55.0%
> 12	9	11.3%
GCS before the operation	9 (IQR 6 - 12)	
≤ 8	32	40.0%
9 - 12	48	60.0%
> 12	0	0 %
Time in hours from stroke to first aspiration (Median)	44.3 (IQR 12 - 165.9)	
Hemorrhage characteristics		
Left-sided hematoma	42 (52.5%)	
Location	Basal ganglia - thalamus	59 (73.7%)
	Lobar	21 (26.3%)
Hematoma volume (mL) before operation	71.9 (IQR 31.7-165.9)	
Midline shift (mm) before operation	10.6 (IQR 5.0 - 16.5)	
Intraventricular hemorrhage *n (%)*	57 (71.3%)	
Graeb score before operation	2.8 (IQR 0 - 8)	

** GCS: Glasgow Coma Scale; SD: Standard deviation; IQR: Interquartile range.*

The mean age of treated patients was 55.6 years (SD 11.4), with 64 males and 16 females. In this cohort, 78.7% of patients (n = 63) had a prior history of hypertension; 10 had been treated pharmacologically. The median pre-operative GCS was 9 (IQR 6 - 12); 21 hemorrhages were lobar and 59 were in the basal ganglia - thalamus. All patients had repeated imaging before surgery; the median pre-operative hematoma volume was 71.9mL (IQR 31.7 - 165.9). The average time from symptom onset until the first aspiration was 44.3 hours (IQR 12 - 165.9 hours). During the treatment period, the median of rt-PA doses was 3 (IQR 1 - 7 doses).

12 months after the procedure, 40 patients (50%) had favorable outcomes (mRS score 0 - 3), and the remaining had poor outcomes (mRS score 4 - 6). 4 patients (5%) had hematoma expansion after the third dose of alteplase. 8 patients with large basal ganglia hemorrhage died within 7 days after symptoms onset. At the 12-month follow-up, 14 patients (17.5%) had achieved good recovery (3 patients mRS 1, 11 patients mRS 2); 16 patients (20%) were severely disabled, and 4 patients (5%) remained vegetative. The overall mortality rate at 12 months after stroke was 25% (20 patients).

Regarding complications after the procedure, post-operative hydrocephalus developed in 3 patients and required a ventriculoperitoneal shunt (VPS) for treatment. Meningitis was observed in 1 patient. Pneumonia and urinary tract infections were each noted in 9 patients, and bacteremia in 3 patients.

** Logistic regression:*

The univariate analysis showed age and neurological status according to GCS score before operation; midline shift on initial head CT scan and final residual hematoma were significant predictors of the outcome within 12 months after ictus. However, the presence of IVH on the initial head CT scan and the location of the hematoma were not significantly associated with the 12-month outcome *(Table 2)*. Next, we analyzed multivariate logistic regression using these variables with the 12-month outcome as the dependent variable. The age of patients (OR = 1.058 per year, 95%CI = 1.007 - 1.112; p = 0.026), the GCS score before operation (OR = 0.666 per one point decrease in GCS score, 95%CI = 0.448 - 0.992; p = 0.046), the initial midline shift (OR = 1.301 per one millimeter increase, 95%CI = 1.057 - 1.601; p = 0.013), and the residual volume hematoma $\geq$ 20mL (OR = 4.402, 95%CI = 1.393 - 13.913, p = 0.012) were the significant predictors of the 12-month poor outcome *(Table 2)*.

Table 2. Logistic regression analysis with the 12-month outcome as the dependent variable.

Variables	Univariate		Multivariate *	
	OR (95%CI)	p	OR (95% CI)	p
Age (per year)	1.073 (1.025 - 1.123)	0.003	1.058 (1.007 - 1.112)	0.026
GCS score on admission (per point)	0.880 (0.714 - 1.085)	0.231		
GCS score before operation (per point)	0.626 (0.447 - 0.876)	0.006	0.666 (0.448 - 0.992)	0.046
Imaging features				
Basal ganglia - thalamus	2.538 (0.895 - 7.202)	0.080		
Presence of IVH	2.400 (0.879 - 6.556)	0.088		
Pre-operative midline shift (per mm)	1.278 (1.073 - 1.522)	0.006	1.301 (1.057 - 1.601)	0.013
Graeb score (per point)	1.184 (0.988 - 1.419)	0.067		
Residual hematoma volume (per mL)	1.038 (1.003 - 1.075)	0.032		
Residual hematoma volume ≥ 20mL	2.914 (1.149 - 7.393)	0.024	4.402 (1.393 - 13.913)	0.012

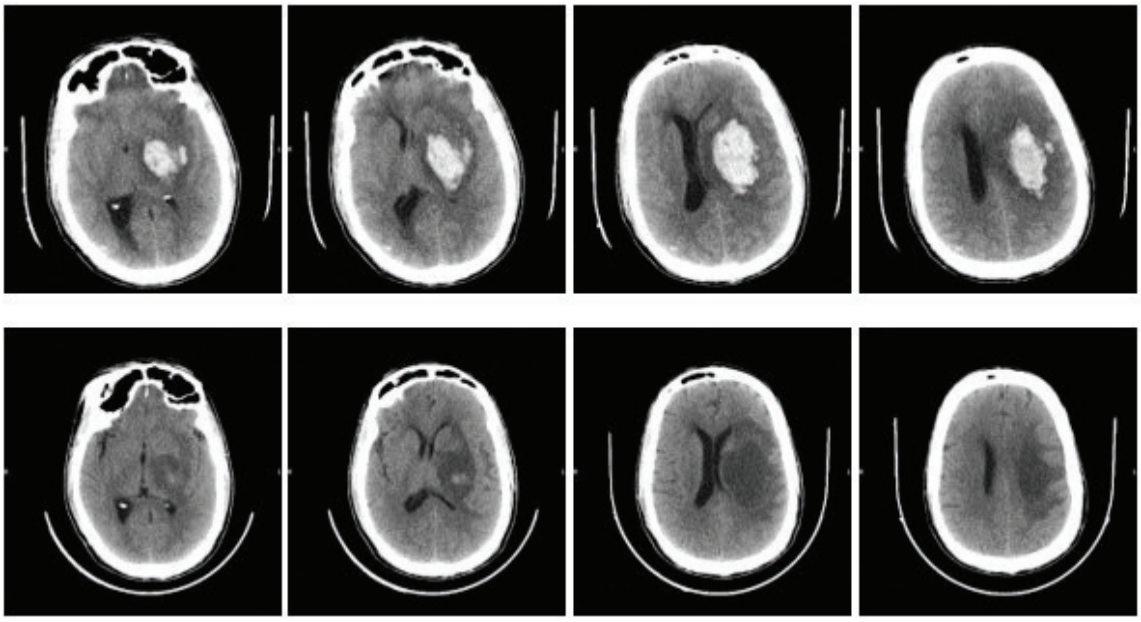

Figure 1. (Top) Admission head CT scan in 58-year-old man demonstrating a left basal ganglia ICH.
(**Bottom**) Head CT scan after withdrawing the catheter.
Note the complete resolution of the ICH.

DISCUSSION

1. Reducing ICH volume and clinical outcome

In recent years, studies of minimally invasive surgery (MIS) with alteplase for supratentorial ICH have shown significantly smaller hemorrhage volumes compared with medical management arms [3, 4]. Montes et al. concluded that CT-guided thrombolysis and aspiration effectively reduced ICH volume by an average of 57% [8]. The MISTIE III was performed in 78 centers with 506 supratentorial hemorrhage patients. Eligibility criteria of the trial were that age ≥ 18 years, ICH volume ≥ 30mL, GCS ≤ 14 or the National Institutes of Health Stroke Scale (NIHSS) score ≥ 6, and the hematoma remained stable (growth < 5mL) for at least 6 hours after diagnostic CT. In this study, the mean reduction in hematoma size was 69% in the MISTIE group compared to 3% in the standard medical care group [3]. Moreover, the results of the MISTIE demonstrated that reduction of hematoma volume to ≤ 15mL is associated with a good functional outcome (mRS 0 - 3), and reducing the hematoma volume by 70% or more increases the chance of achieving a good outcome [3]. In our

study, the median hematoma volume (71.9mL) was more significant than that in the MISTIE III (41.8mL). Despite variations in procedure and patient selection, the mean final ICH volume was 23.9mL (SD 24.6), with ICH volume reduction by an average of 66%, which was consistent with the previously reported case series. Although rebleeding was a concern in minimally invasive hematoma evacuation, we documented 4 instances (5%) of hematoma growth after the third dose. Patients with hematoma expansion during treatment were closely monitored. In addition, there was no clinical deterioration from edema or mass associated with residual hematoma.

Clinically, the patients in our study exhibited a trend toward improvement, with GCS scores improving in all patients. However, 8 patients with large basal ganglia hemorrhage died within 7 days after symptoms onset.

2. 12-month outcomes and logistic regression

Regarding long-term outcomes, 50% of patients had unfavorable outcomes; 14 patients (17.5%) in our series achieved good recovery; 16 patients (20%) were severely disabled; and 4 four patients (5%) remained vegetative.

Many studies have been conducted to assess the safety and efficacy of minimally invasive catheter placement and hematoma drainage with ICH. However, more research is needed to identify the factors that affect the hematoma evacuation. Therefore, our study analyzed and identified possible clinical and radiological factors for prognosis within 12 months. In relation to possible prognostic risk factors for 12-month outcomes, our work demonstrated that neurological status according to GSC score before the operation, middle line shift, and residual hematoma volume were significant predictors of poor outcomes. In many studies that are consistent with our results, a higher GCS immediately before surgery has been shown to be a predictor of a better outcome after surgery. In a meta-analysis of randomized controlled trials in 2012, Zhou X. et al. demonstrated that patients with supratentorial ICH might benefit more from MIS than other treatment options [9].

As the population ages, an increasing number of older individuals with intracranial hematomas eligible for surgical treatment will probably be encountered. In our material, we found a statistically significant correlation between age and outcome within the long-term follow-up period in this study *(Table 2)*. Some studies reported that age was one of the factors predicting

the outcome after surgery for ICH [3]. It can be explained that younger patients do not suffer brain atrophy found in older age; therefore, any added hematoma volume would dramatically increase intracranial pressure (ICP) in the already tight intracranial cavity, making the beneficial effect of surgery realized.

Pre-operative midline line shift was also discovered to be a significant prognostic factor for post-operative outcome at 12 months following the surgery, where poor outcome correlated positively with increasing middle line shift (*Table 2*, p = 0.013). Similar results have been reported by other publications. For instance, early survival was associated with morphologic characteristics of the initially computed tomogram, such as the degree of midline shift in the study by Daverat et al. [2]. The degree of midline shifts, both pre-operatively and post-operatively, was also cited by Moussa et al. as a significant predictor of post-operative outcomes in patients undergoing decompressive craniectomy [10].

It has been well-documented that hematoma volume of ICH is associated with patient outcomes. Sirh S. et al. concluded that the only factor affecting the post-operative 6-month neurologic outcome is the final volume of remaining hematoma after drainage in patients with spontaneous supratentorial ICH who underwent stereotactic aspiration [4]. As mentioned above, the results of MITIE III also determined that a more significant ICH reduction has a higher likelihood of achieving mRS of 0 - 3, with a minimum evacuation threshold of ≤ 15mL. Patients with a hematoma volume reduction of 70% and more increase the chance of achieving a good outcome [3]. Choo et al. suggested a good clinical outcome, according to mRS, can be expected after stereotactic catheter drainage in patients with a hematoma volume between 20 - 30mL [5].

CONCLUSION

In supratentorial ICH, adding stereotactic CT-guided aspiration and rt-PA to hematoma evacuation is safe and effective for ICH evacuation. Additionally, it contributes strongly to a better outcome in the selected group of patients. In general, older age, lower GCS immediately before surgery, maximal pre-operative midline shift, and residual hematoma volume ≥ 20mL were unfavorable prognostic factors for long-term outcomes. The findings in our study may help physicians to recognize patients-specific predictive factors for poor outcomes.

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