European Review for Medical and Pharmacological Sciences 2018; 22: 4663-4668

Clinical study on the early application and ideal dosage of urokinase after surgery for hypertensive intracerebral hemorrhage

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Abstract. – OBJECTIVE: The objective of the present study was to investigate the clinical efficacy of early application and ideal dosage of urokinase after minimally invasive surgery for hypertensive intracerebral hemorrhage (HICH).

PATIENTS AND METHODS: We consecutively enrolled 132 patients with HICH who underwent CT-guided stereotactic intubation of the hematoma combined with dissolution using urokinase, where the urokinase was injected at 24 h after intubation. The 40 patients in the low-dosage group received 10-30 thousand units of urokinase; the 46 patients in the moderate-dosage group received 40-60 thousand units of urokinase; and the 46 patients in the high-dosage group received 70-100 thousand units of urokinase. After the drainage tubes were clamped for 4-6 h, clamps were removed for drainage for 24 h, and the intubated tubes were maintained for 3-5 d. Patients in all groups were followed up for 6 months, and the clinical outcomes were compared.

RESULTS: The clearance of hematomas in the high-dosage group was significantly improved compared with the other two groups ($p<0.05$), and the occurrence rates of complications in the moderate- and high-dosage groups were significantly higher than in the low-dosage group ($p<0.05$). During follow-up, the Chinese stroke scale and Barthel index scores in the high-dosage group were higher than those in the other two groups ($p<0.05$). The serum levels of matrix metalloproteinase-9 (MMP-9) and neuron-specific enolase (NSE) in the high-dosage group were lower than those in the other two groups ($p<0.05$).

CONCLUSIONS: CT-guided stereotactic intubation of the hematoma combined with dissolution using urokinase is effective for eliminating the hematoma for treatment of HICH with few complications. For recovery of neurological functions and improvement of regular life skills, it is considered to be associated with decreases in the serum levels of MMP-9 and NSE.

Key Words
HICH, Stereotactic, Urokinase, Dosage, MMP-9, NSE.

Introduction

Hypertensive intracerebral hemorrhage (HICH) accounts for roughly 30-60% of cases of intracerebral hemorrhage, and is characterized by rapid progression, and high mortality and disability rates[1]. The clinical prognosis is correlated with the site and volume of hemorrhage as well as the methods and duration of treatment[2]. Superior efficacy has been observed with CT-guided stereotactic intubation of the hematoma for drainage combined with dissolution using urokinase, compared with conservative drug treatment, hematoma clearance by craniotomy, and external ventricular drainage[3]. In addition, minimally invasive surgeries can be divided into two kinds with varying advantages and disadvantages[4], i.e., the hard tunnel and soft tunnel. As a direct plasminogen activator with no antigenicity or toxicity, urokinase can rapidly dissolve residual hematomas by injection into the hematoma or by rinsing the cavity of the hematoma, shortening the duration of drainage, which is of great significance for recovery of neurological functions and improvement of survival and prognosis[5]. Moreover, scholars[6] reported that equivalent or higher efficacy was achieved with recombinant tissue plasminogen activator (rt-PA), compared with urokinase. However, there remains no unified understanding of the application time of urokinase. Some authors believe that the application of urokinase within 24 h (especially between 6 and 12 h) after intubation can significantly lower the hematoma volume with no increase in the occurrence of recurrence of hemorrhage or infection[7]. In contrast, others believe that urokinase should be applied after 24 h for better safety[8]. There is also controversy regarding the application dosage of urokinase[9]. Various dosages of urokinase, such as 10-30 thousand units, 40-60 thousand units, and 70-100 thousand units are currently being used. In this work, we analyzed

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the clinical outcomes of the early application of varying dosages of urokinase for the treatment of HICH, to provide a reference for the selection of appropriate treatment procedures.

Patients and Methods

Patients

We consecutively enrolled a total of 132 patients who were diagnosed for the first time with HICH in our hospital (Dongying, Shandong, China) between January 2013 and January 2016. The inclusion criteria were as follows: a) patients were aged from 18-70 years old; b) patients whose diagnosis was confirmed through CT examination, where according to the Dorian formula (volume of hematoma = ABC/2), the supratentorial hematoma volume was not larger than 30 ml, and the infratentorial hematoma volume was not larger than 15 ml; c) patients with disease time no longer than 72 h, surgical indications, and anticipated efficacy; d) patients whose clinical data were complete and who provided informed consent. The exclusion criteria were as follows: a) patients who had intracerebral hemorrhage, brain tumors, cerebrovascular malformation, or intracranial aneurysm; b) patients who were allergic to urokinase, or had a recent history of major surgery or severe gastrointestinal ulcer; c) patients who were in severe condition with an anticipated survival period less than 3 months. The study was approved by the CCS Committee of People Hospital Dongying City.

According to the dosage of urokinase, the 136 patients were divided into 3 groups, i.e., the low-dosage group (n = 40, 10-30 thousand units of urokinase), the moderate-dosage group (n = 46, 40-60 thousand units of urokinase), and the high-dosage group (n = 46, 70-100 thousand units of urokinase). In the low-dosage group, there were 26 males and 14 females, with an average age of 56.2 ± 17.5 years, average disease time of 6.6 ± 2.5 h, average supratentorial hematoma volume of 21.3 ± 6.8 ml, average infratentorial hematoma volume of 11.2 ± 5.4 ml, and average Glasgow Coma Scale (GCS) score of 12.5 ± 4.6. Among these patients, there were 25 with basal ganglia hemorrhage, six with ventricular hemorrhage, six with lobar hemorrhage, and three with cerebellar hemorrhage. In the moderate-dosage group, there were 29 males and 17 females, with average age of 55.6 ± 16.7 years old, average disease time of 6.8 ± 2.6 h, average supratentorial hematoma volume of 23.4 ± 9.2 ml, average infratentorial hematoma volume of 10.5 ± 5.2 ml, and average GCS score of 11.6 ± 4.9. Among these patients, there were 30 with basal ganglia hemorrhage, 7 with ventricular hemorrhage, 5 with lobar hemorrhage, and 4 with cerebellar hemorrhage. In the high-dosage urokinase group, there were 30 males and 16 females, with average age of 57.8 ± 19.3 years old, average disease time of 7.2 ± 2.9 h, average supratentorial hematoma volume of 20.8 ± 9.3 ml, average infratentorial hematoma volume of 11.8 ± 5.6 ml, and average GCS score of 10.8 ± 5.5. Among these patients, there were 32 with basal ganglia hemorrhage, 6 with ventricular hemorrhage, 4 with lobar hemorrhage, and 3 with cerebellar hemorrhage. The baseline parameters of the three groups were comparable.

Methods

Positive medical treatment procedures were applied to all patients, including reducing the intracranial pressure, prophylaxis of infections, fluid infusion, nutritive support, and temperature control. For surgical methods, we applied CT-guided stereotactic intubation of the hematoma plus dissolution using urokinase while the patients were under general anesthesia. During surgery, we applied an ASA-602S high precision stereotaxic apparatus (Shenzhen Anke High-tech Co., Ltd, Shenzhen, Guangdong, China) and a Siemens (Erlangen, Germany) SOMATOM Sensation 64 CT Scanner (layer thickness: 2 mm) for head scans, in which the x, y, and z coordinates were calculated with the lower part of the hematoma as the origin. For patients with basal ganglia hemorrhage or ventricular hemorrhage, we performed drilling through the forehead, in which the drilling point was located at the site 1.5 cm inside the hairline and 2.5-3.5 cm from the midline, and the diameter of the drilling hole was 4 mm. For patients with lobar hemorrhage, the drilling point was located in the part of the hematoma near the skull, avoiding the important vessels and functional areas inside the head. For patients with cerebellar hemorrhage, drilling through the cranial fossa was performed with the drilling point beginning at the site 2.5 cm beneath the superior nuchal line on the hemorrhage side and 3.5-5.0 cm from the midline. Under the instruction of a coordinate positioning guider, the silica-gel ventricular drainage tube (inner diameter: 2.5 mm) was inserted into the guider and gradually positioned to the center of the hematoma. Lateral external ventricular drainage was also conducted for patients whose hematoma was ruptured and with

content that released into the ventricles. The empty injector which was connected to the drainage tubes was dragged slowly for extraction of the hematoma, in which the first extraction, according to the degree of organization of the hematoma, was around 1/3-1/2 of the total hematoma.

At 24 h after surgery, head CT scans were performed again to identify the position of the drainage tube and the volume of residual hematoma. The criteria for application of urokinase were as follows: the residual supratentorial hematoma volume was not less than 15 ml, and the residual infratentorial hematoma volume was not less than 10 ml. Varying dosages of urokinase were injected through the drainage tubes 1 time/day, followed by clamping of the drainage tubes for 4-6 h, removing the clamps for 24 h of drainage, and intubation for 3-5 days.

Observational Indexes

We compared the differences in hematoma clearance, occurrence rate of complications, neurological function defect, regular life skills, and the serum levels of matrix metalloproteinase-9 (MMP-9) and neuron-specific enolase (NSE) among the groups. The ratio of the final residual hematoma to the residual hematoma after the first extraction was set as the criterion for comparison of hematoma clearance, which was further divided into the following grades: basically eliminated (5-10%), mostly eliminated (10-30%), partially eliminated (30-90%), and re-bleeding (no less than 90%). The follow-up duration was set as 6 months, during which we employed the Chinese stroke scale (CSS) for assessment, including a total of eight parameters: consciousness (0-9 points), horizontal gaze function (0-4 points), facial muscles (0-2 points), language (0-6 points), muscle strength of upper extremities (0-6 points), manual muscle strength (0-6 points), muscle strength of lower extremities (0-6 points), and walking function (0-6 points). The highest score was 45 points and 0-15 points represented mild type, 16-30 points represented moderate type, and 31-45 points represented severe type. Barthel index (BI) was applied to assess regular life skills with scores ranging from 0-100 points. Patients with a score 60 or more points were characterized by mild dysfunction but able to independently accomplish regular activities in addition to some circumstances that required help from others. Patients with a score from 41 to 60 points were considered to have moderately recovered but with moderate dysfunction, and only able to complete regular activities with substantial help from others. Patients with scores less than 41 points were considered as poorly recovered and unable to accomplish most regular activities without help from others. We also measured the serum levels of MMP-9 and NSE by ELISA (Enzyme-linked immunosorbent assay). The ELISA kit was from Jiangsu Beyotime Biotechnology Co., Ltd (Nanjing, Jiangsu, China) and all procedures were performed strictly according to the manufacturer's instructions.

Statistical Analysis

SPSS20.0 software (IBM SPSS Statistics for Windows, Armonk, NY, USA) was used for data analysis. Numerical data are presented as mean ± standard deviation. Independent sample t-test or one-way ANOVA was conducted for intergroup comparisons, LSD *t*-test was used for paired comparisons, and paired *t*-test was used for intragroup comparisons. Categorical data are presented as cases or percentage. A χ^2-test was performed for intergroup comparisons, and rank sum test was performed for comparison of ranked data. $p<0.05$ suggested that the difference was statistically significant.

Results

Comparison of Hematoma Clearance Effect

Hematoma clearance in the high-dosage group was superior to those in the other two groups, and the differences were statistically significant ($p<0.05$) (Table I).

Comparison of the Occurrence Rates of Complications

The occurrence rates of complications in the moderate- and high-dosage groups were significantly lower than in the low-dosage group ($p<0.05$) (Table II).

Comparisons of CSS and BI Scores

CSS and BI scores of the high-dosage group during follow-up were significantly higher than in the other two groups ($p<0.05$) (Table III).

Comparisons of the Levels of MMP-9 and NSE

The serum levels of MMP-9 and NSE in all three groups after treatment were significantly lower than those before treatment, and the levels in the high-dosage group were significantly lower than those in the other two groups ($p<0.05$) (Table IV).

Table I. Comparison of hematoma clearance [cases (%)].

Group	Case	Basically eliminated	Mostly eliminated	Partially eliminated	Re-bleeding
Low-dosage group[a]	40	15 (37.5)	10 (25.0)	12 (30.0)	3 (7.5)
Moderate-dosage group[b]	46	20 (43.5)	15 (32.6)	9 (19.6)	2 (4.3)
High-dosage group	46	33 (71.7)	9 (19.6)	3 (6.5)	1 (2.2)

Note: [a], comparison between the low-dosage group and high-dosage group, Z=−3.473, p=0.001; [b], comparison between the moderate-dosage group and high-dosage group, Z=−2.787, p=0.005.

Table II. Comparison of hematoma clearance [cases (%)].

Group	Cases	Re-bleeding	Infection	Hydrocephalus	Death	Occurrence rate of complications
Low-dosage group	40	3	2	3	2	10 (25.0)
Moderate-dosage group[#]	46	2	1	1	0	4 (8.7)
High-dosage group[*]	46	1	1	1	0	3 (6.5)

[#], comparison between the low-dosage group and moderate-dosage group, χ^2=4.173, p=0.041; *, comparison between the low-dosage group and high-dosage group, χ^2=5.693, p=0.017.

Table III. Comparisons of CSS and BI scores.

Group	Cases	CSS scores	Mild	Moderate	Severe	BI scores	Good	Moderate	Poor
Low-dosage group	40	26.6±4.9[a]	22 (55.0)	10 (25.0)	8 (20.0)	64.4±17.8[aa]	25 (62.5)	9 (22.5)	6 (15.0)
Moderate-dosage group	46	17.5±4.7[b]	26 (56.5)	15 (32.6)	5 (10.9)	72.3±15.6[bb]	30 (65.2)	12 (26.1)	4 (8.7)
High-dosage group	46	14.8±4.6	38 (82.6)	6 (13.0)	2 (4.3)	85.5±12.3	40 (87.0)	4 (8.7)	2 (4.3)

Note: [a], comparison of CSS scores between the low-dosage group and high-dosage group, t=15.632, p<0.001, comparison of the ranked data, Z=−2.873, p=0.004; [b], comparison between the moderate-dosage group and high-dosage group, t=6.532, p=0.008, Z=−2.671, p=0.008; [aa], comparison of BI scores between the low-dosage group and high-dosage group, t=−12.635, p<0.001, Z=−2.628, p=0.009; [bb], comparison between the moderate-dosage group and high-dosage group, t=−8.632, p<0.001, Z=−2.371, p=0.018.

Table IV. Comparisons of the levels of MMP-9 and NSE (μmol/l)..

Group	MMP-9		NSE	
	Before treatment	After treatment	Before treatment	After treatment
Low-dosage group	356.2±83.4	223.5±92.7	156.9±72.3	125.8±52.6
Moderate-dosage group	364.8±72.3	198.7±86.4	152.8±59.2	103.4±42.5
High-dosage group	372.5±66.5	165.4±82.5	165.4±65.3	86.7±35.4
F	0.265	5.968	0.193	5.324
p	0.856	0.003	0.921	0.008

Discussion

Cerebral hemorrhage can cause primary and secondary cerebral damage[10]. The primary type can exhibit the mass effect in a short time after the hemorrhage, leading to mechanical suppression and laceration of cerebral tissue. Secondary damage, namely hydrocephalus and hematoma, causes the massive release of vasoactive factors such as kinin, histamine, and 5-hydroxytryptamine. This, in turn, triggers vasoconstriction, further aggravating responses of cerebral cells, such as ischemia, hypoxia, dysfunction of energy metabolism, oxidative stress, inflammation, and apoptosis of neurons, thereby exacerbating the recovery of neural functions and increasing the

disability and mortality rates. Surgery performed at an ultra-early stage (within 6 h) can result in the hematoma mass blocking the side hole of the drainage tube, which cannot be easily dissolved using urokinase. In addition, the occurrence rates of re-bleeding and infection increase. However, within 12-24 h, part of the hematoma is liquidized, the patient is in a relatively stable condition, and the shape of edema surrounding the hematoma can be easily identified. Also, the bleeding site is already blocked; therefore, 12-24 h may be the ideal time to perform stereotactic surgeries[11].

With various advantages, such as high precision and minimal invasion, CT-guided stereotactic intubation of the hematoma combined with dissolution using urokinase can be utilized for the treatment of hematomas located in the deep part or major functional areas of the brain. However, it also has disadvantages, such as the requirement for specific stereotactic apparatus, complex procedures, excessively long preoperative preparation time, and the need for CT scan guidance. In addition, it is not applicable for cerebral hemorrhage patients with severe intracranial hypertension who require emergency treatment[12]. The purpose of the first extraction after intubation is to release the suppression of surrounding cerebral tissues, which is of great significance for the prophylaxis of cerebral hernia. However, after extraction of the hematoma, the negative pressure inside the hematoma can easily induce re-bleeding[13]. Urokinase facilitates the decomposition and liquidation of blood clots by resolving their fibrin skeleton. It only acts focally and is safe, without affecting the coagulation system[14,15].

In the present study, we found that hematoma clearance in the high-dosage group was superior to the other two groups, and the occurrence rates of complications in the moderate- and high-dosage groups were significantly lower than in the low-dosage group. During the follow-up period, the CSS and BI scores in the high-dosage group were significantly higher than those in the other two groups, and the serum levels of MMP-9 and NSE in the high-dosage group were significantly lower than those in the other two groups, indicating that the application of high-dosage urokinase for treating HICH has a better clearance effect, reduces the occurrence rates of complications, facilitates the recovery of neurological functions, and improves regular life skills, which may be correlated with the decreased serum levels of MMP-9 and NSE. In addition, we found that extending the clamping time of drainage tubes can reduce the application times and dosages of urokinase, indicating that the action time of urokinase was also associated with hematoma clearance[16]. The re-bleeding induced by the dissolution of hematomas using urokinase is considered to be related to the damage of blood-brain barriers. MMP-9, as a Zn^{2+}-dependent endopeptidase, can decompose the major components of the basal membrane of cerebral vessels to induce vasogenic hydrocephalus and the transformation into cerebral hemorrhage[17]. In normal brain tissue, there is no or little expression of MMP-9. However, in cerebral infarction, the expression of MMP-9 is increased in the vascular endothelium and in glial cells surrounding the lesion after ischemia-reperfusion, further increasing the permeability of blood-brain barriers. After thrombolysis using urokinase, we observed the expression of MMP-9 in the lateral ischemic hemisphere[18]. NSE activity is distributed mostly in oligodendrocytes, neuroendocrine cells, and neurons, and can reflect the degree of injury of neurons at an early stage after cerebral hemorrhage. It can be used for predicting the clinical prognosis with high sensitivity and specificity[19,20].

Conclusions

For HICH patients with surgical indications, the time of surgery must be selected rationally. Minimally invasive surgery should be applied for decreasing the pressure and for drainage, and intubation inside the hematoma should be performed at an early stage for dissolving the blood clot through injection of a high dosage of urokinase. These procedures have great application value for improving clinical symptoms and prognosis. In future studies, we will further verify this conclusion by increasing the sample-size and extending the follow-up period.

Conflict of interest

The Authors declare that they have no conflict of interests.

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