Revista Argentina de Clínica Psicológica
2020, Vol. XXIX, N°5, 1271-1280
DOI: 10.24205/03276716.2020.1122

Efficacy of Minimally Invasive Endoscopic Neurosurgery (MIEN) and Urokinase Perfusion Treating Hypertensive Intracerebral Hemorrhage（HICH）

Ximei Xie[ae], Wenyang Zhu[be], Su-e Xu[c], JianCheng Wang[d*]

Abstract

Objective: To investigate the efficacy and prognostic value of minimally invasive endoscopic neurosurgery (MIEN) and urokinase perfusion treating hypertensive intracerebral hemorrhage（HICH）Methods: A total of 158 patients with HICH were recruited in this cohort from May 2016 to March 2017, with 80 cases underwent combined treatment of MIEN and urokinase perfusion employed as combined group and 78 cases underwent traditional craniotomy as control group. Hs-CRP, IL-11 and NLR before and after treatment of both groups were detected using ELISA, and a comprehensive set of clinicopathological data such as therapeutic effect, perioperative indicator, complication and prognosis were evaluated.

Results: NIHSS scores and serum hs-CRP, IL-11, and NLR of two groups decreased significantly after treatment (P<0.05), meanwhile, the combined group showed a lower level than the control group (P<0.05); In addition, the control group had a longer operation time, lower hematoma clearance rate, larger intraoperative blood loss, longer hospital stay, higher complication rate and lower GOS rate compared with the combined group(P<0.05). Poor prognosis of patients with hypertension history, age＞60, hematoma volume＞50 ml and GCS score ≤ 5 after combined treatment were considered as independent risk factor (P < 0.05).

Conclusion: Combined treatment of MIEN and urokinase perfusion could exert a more preferable curative effect on HICH than conventional surgery, reduce the incidence of complications as well as inflammation, and improve surgical process and prognosis.

Keywords： MIEN ; urokinase ; HICH ; inflammation ; prognosis

Introduction

Hypertension, as the most important risk factor for intracerebral hemorrhage, has made it a disease with extremely high mortality and morbidity. Patients often need to bear very high medical costs during the treatment process while the prognosis is still not optimistic [1]. HICH is mainly attributed to changes in secondary hypertension and abnormal arteriolar rupture of other blood vessels, of which the incidence can be reduced by blood pressure control in some developed countries, though, the incidence rate of HICH is still soaring up in developing countries, accounting for 10-24% of stroke patients worldwide [2]. Even if the patient survives after treatment, serious neurological sequelae would occur at later stage, which would exert great impact on the prognosis and life of the patient [3]. Studies have shown that surgical drainage has higher clinical value than medical treatment when intracerebral hematoma is shown to be large [4]. In the past, traditional craniotomy served as a straw for most HICH patients to clutch at, which could decrease the mortality rate and improve the poor prognosis of patients [5], and moreover, effectively remove hematoma.

[a] Department of Acupuncture Massage and Rehabilitation, Xi'an Hospital Of Traditional Chinese Medicine,Xi'an,China
[b] Department of Interventional Radiology, Huai'an Second People's Hospital and The Affiliated Huaian Hospital of Xuzhou Medical University, Huai'an,China
[c] Department of Internal Medicine-Cardiovascular, Huai'an Hospital of Traditional Chinese Medicine, Huai'an,China
[d] Department of Invasive Technology, Lianshui County People's Hospital,LianShui,China
[e] contribute equal to this article as co-first author
**Corresponding Author: JianCheng Wang Address: Department of Invasive Technology, Lianshui County People's Hospital,LianShui,China Email: rongtuanche9316@163.com*

Nevertheless, the operation of tratitional craniotomy would often damage the surgical path and surrounding brain tissue, induce various complications and affect the prognosis of patients [6].

Neuroendoscopy, as a new type of minimally invasive surgery, has been frequently applied in the minimally invasive surgery in recent years. In contrast to conservative treatment and traditional craniotomy, it can effectively reduce the rate of rebleeding and mortality and reduce the tissue damage of patients. However, there still exists controversies on the efficacy and patient's prognosis of MIEN surgery [7-8]. Urokinase perfusion therapy is currently considered to be a less invasive treatment of intracerebral hemorrhage with high thrombolytic efficiency, more safety, low mortality and rebleeding rate, and morever, less damage to brain tissue than conventional surgery [9]. Yet there are few studies on the combined treatment of MIEN and urokinase perfusion on HICH disease. In order to explore a highly effective and safe treatment for HICH patients, we will elaborate on the combined treatment to determine whether it was superior to the traditional craniotomy and could improve prognosis and complication, aiming to provide a reference for clinical research.

1 Materials and Methods

1.1General Information

A total of 158 HICH patients aged from 55 to 70 were recruited in this cohort from May 2016 to March 2017, with an average age of 54.78±8.24, 72 cases of male and 86 cases of female. Patients were divided into combined group (80 cases) and control group (78 cases) according to the surgery they underwent. The general information of two groups of patients is shown in Table

Inclusion criteria: (1) Confirmed diagnosis of hypertensive cerebral hemorrhage by clinical, biochemical and imaging examinations and conformity to the diagnostic criteria for cerebral hemorrhage[10]; (2) Initial treatment in our hospital for all patients with admission time within 72 hours and age not exceeding 75; (3) Glasgow Coma Scale (GCS score)[11]≤ 12 points, the amount of supratentorial cerebral hemorrhage > 30 ml, and the amount of cerebral hemorrhage under the curtain > 10 ml.

Exclusion criteria: Patients (1)with serious diseases such as brain stem hemorrhage, arteriovenous malformation, etc. and a survival period of no more than 6 months ; (2) with combination cardiac or/and hepatorenal insufficiency and coagulation dysfunction; (3) with anesthesia contraindications and cannot tolerate tracheal intubation for general anesthesia.

This research has been approved by the Medical Ethics Association of the department, subjects of both groups were well informed of the details and procedures in the experiment and signed the informed consent.

1.2 Therapeutic Method

1.2.1 Combined treatment of MIEN and urokinase perfusion

Central point of hematomas was located using cranial computed tomography. A longitudinal incision, which was bone foramen-centered, was performed avoiding important blood vessel and functional domain. With skull drilling diameter of 1.5-2.5cm, bone window was appropriately opened. Endocranium was cut with a crossed incision, and bipolar coagulation was applied to stanch bleeding of brain surface. After a short cut avoiding cortical vessel, haematoma cavity was pierced using disposable puncture catheter under the guide of CT. With inner core of the catheter pulled out and its transparent drivepipe retained and fixed by S-shaped retractor, 0° endoscope were placed to absorb and remove cerebral hematomas as much as possible under endoscopic direct vision. After confirming that the cavity wall at all angles was completely cleaned up, the endoscope was withdrawn, and a drainage tube with side holes was retained to connect the drainage bag with three-way valve which was suspended from the lower position to facilitate drainage. 3 hours after surgery, 20,000U urokinase was diluted with 5 ml of physiological saline to dissolve the blood clot through three-way valve, and the valves were reopened after being clamped for 2-3 hours. With this procedure repeated twice a day, basic drainage would be completed after 3-5 days.

1.2.2 Traditional Craniotomy

The hematoma center was determined by Cranial CT, with surgical incision located in the closest point to the scalp and avoiding important functional domain and blood vessels, a 6cm U-shaped incision was performed under the microscope. The area from the skin to the aponeurosis was cut up successively, the periosteum was peeled along the incision, the bone flap was removed and the bone hole was drilled. A 3cm bone window was opened and suspended, the endocranium was cut up avoiding the cortical blood vessels with star-like incision, the cortex was incised along the direction of the gyrus and fully flushed under the microscope. The hematoma was removed and stanched by bipolar coagulation. After the completion of the placement of the drainage tube, the cranium was closed using conventional suture with the facilitation of hemostatic yarn. The operation of both groups was performed under general anesthesia with tracheal intubation, and the drainage tube was removed 3-7 days after surgery.

Fasting venous blood were collected from all patients before and after treatment and placed for 15-30 min at 4℃, and then centrifuged at 3000rpm for 10 min. Serum were carefully extracted from the upper liquid and stored at -80℃separately. Sample, standard and blank wells were prepared on the 96-well ELISA plate, standards were diluted in strict accordance with kit instructions, 100μl standards and samples were added to the corresponding wells, sealed and incubated for 2h. Then the plate was washed for 5 times. 100μl prepared anti-biotin were added into each well of sample and standard, and incubated for 1h and washed for 5 times again. 100μl HRP(horse radish peroxidase) labeled Streptavidin were filled into each well and washed for 5 times. TMB coloring solution were added into each well and placed for 20 min. at door temperature in the dark place for color reaction. At last, A450 value was measured using microplate reader, standard curve was plotted, and the sample concentration was calculated according to the absorbance value and the standard curve. Hs-CRP ELISA kit, TMB coloring solution, and microplate reader was purchased from Shanghai Biyuntian Biotechnology Co., Ltd. (Cat. No. PC190, P0209, E1140) and IL-11 ELISA kit from Shanghai Zhenyu Biotechnology Co., Ltd. E-EL-H5022km-1).

1.3 Observation indicators

The National Institute of Health stroke scale (NIHSS) was used to evaluate the neurological function of patients before and after treatment, and the effect was evaluated by comparing the changes of NIHSS score after surgery. With the standard of reduction of 91-100% as cured and 18-90 % as effective, increase or decrease of 0-17% as invalid, and the total effective rate of treatment as (cured + effective) / total number * 100%, perioperative indicators of patients were recorded (operative time, hematoma clearance rate, intraoperative blood loss, hospitalization Time, reoperation rate), neutrophil to lymphocyte ratio (NLR) in peripheral blood and HS-CRP, IL-11 concentration before treatment and 7 days after treatment were analyzed. All patients are required to attend subsequent visit within 3 months after treatment, regular telephone follow-up was performed and cases of complication was collected, prognosis of patients were evaluated according to GOS grading standards, with level I for death, level II for minimum response of vegetative state, level III severe disability, level IV mild disability, level V good recovery , and the GOS excellent rate (IV level + V level) / the total number of cases * 100%.

1.4 Statistical Approach

All statistical analyses in this study were performed using the SPSS21.0（SSPSS Inc., Chicago,IL,USA）statistical software package and plotted using GraphPadPrism8.0（Huanzhongruichi Science and technology Co. Ltd, Beijing, China.）. in which enumeration data was presented in terms of percentage and χ^2 was applied in group comparison; measurement data was presented in terms of （x±sd）and independent-sample T test was applied in group comparison. Multi-factors were analyzed using logistics regression model, and p value less than 0.05 was considered as statistical significance.

2 Results

2.1 Comparison of general information

The general clinical data of the two groups were compared and no significant differences in age, gender, bleeding position, hematoma volume, admission GCS score and hypertension history appeared between two groups (P>0.05). See Table 1 for details.

2.2 Comparison of curative effects

According to the changes of NIHSS scores, the efficacy of the patients was better than that of the control group (P<0.05). The total effective rate in the combined group (71.25%) was higher than that of the control group (52.56%) (P<0.05). There was no significant difference in the NIHSS score before treatment(P > 0.05). NIHSS scores were lower than those before treatment (P<0.05). After treatment, the NIHSS scores of the two groups were lower than those of the control group (P<0.05) See Table 2 for details.

2.3 Comparison of surgical indicators

Intraoperative blood flow, surgical result and postoperative indexes were compared between patients in two groups treated with different surgical methods. The results showed that compared with the combined group, the control group had longer operation time and lower hematoma clearance rate, larger amount of bleeding and the longer length of hospital stay

(P<0.05). There was no significant difference in reoperation rate between two groups (P>0.05). See Table 3 for details.

Table 1. **Comparison of general information between two groups [n (%)]**

Clinical factors	Combined group (n=80)	Control group (n=78)	χ^2	P
Age of years			0.20	0.649
> 60	31 (38.75)	33 (42.31)		
≤60	49 (61.25)	45 (57.69)		
Gender			0.02	0.884
male	44 (55.00)	42 (53.85)		
female	36 (45.00)	36 (46.15)		
Bleeding location			1.579	0.454
cortex	17 (21.25)	20 (25.64)		
basement	33 (41.25)	36 (46.15)		
others	30 (37.50)	22 (28.21)		
Volume of hematomas (ml)			0.358	0.550
≤50	55 (68.75)	57 (73.08)		
> 50	25 (31.25)	21 (26.92)		
Admission GCS score (point)			0.400	0.527
≤5	43 (53.75)	38 (48.72)		
> 5	37 (46.25)	40 (51.28)		
History of hypertension			0.100	0.752
without	17 (21.25)	15 (19.23)		
with	63 (78.75)	63 (80.77)		

Table 2. **Comparison of efficacy evaluation between two groups of patients (x ± sd) [n (%)]**

Group	curative effect				NIHSS score	
	cured	improved	invalid	total effective rate (%)	Prior treatment	Post-treatment
Combined group (n=80)	33 (41.25)	24 (30.00)	23 (28.75)	71.25 (57/80)	35.12±5.17	8.14±2.51*
Control group (n=78)	21 (26.92)	20 (25.64)	37 (47.44)	52.56 (41/78)	34.85±5.23	14.62±3.52*
t/χ^2	6.273			5.855	0.326	9.968
P	0.043			0.016	0.745	<0.001

Note: The NIHSS score of the combined group (t=40.700, P<0.001) and the control group (t=34.350, P<0.001) both decreased after treatment.

Table 3. **Comparison of surgical indicators between two groups (x ± sd) [n (%)]**

Group	Operation time (min)	Hematomas clearance rate (%)	Intraoperative bleeding (ml)	length of stay (d)	Reoperation rate (%)
Combined group (n=80)	51.79±14.68	94.62±6.23	48.25±6.82	15.71±3.64	2.50 (2/80)
Control group (n=78)	186.64±24.62	86.82±5.14	354.71±37.91	27.34±5.81	7.69 (6/78)
t/χ2	41.940	8.573	71.14	15.12	2.215
P	P<0.001	P<0.001	P<0.001	P<0.001	0.137

2.4 Changes in inflammatory factors before and after treatment

The changes of inflammatory factors in two groups before and after treatment were analyzed according to the results of ELISA and the ratio of NLR in peripheral blood. There was no significant difference in serum HS-CRP, IL-11 and NLR between two groups before treatment (P>0.05) while the serum levels of HS-CRP, IL-11 and NLR of both groups decreased after treatment (P<0.05), and serum levels of HS-CRP, IL-11 and NLR in the combined group were lower than those in the control group (P<0.05). See Table 4 for details.

2.5 complications

All postoperative complications of patients were collected. The incidence of Intracerebral infection, pulmonary infection, severe pain, Intracerebral rebleeding and water-electrolyte disturbance in the combined group was significantly lower than that in the control group (P<0.05). There was no significant difference in the incidence rate of malnutrition between two groups(P>0.05), and the incidence of complications in the combined group was lower than that in the control group, See Table 5 for details.

Table 4. **Comparison of inflammatory factors of two groups before and after treatment (x±sd)**

Inflammatory index		Prior treatment	Post-treatment	t	P
HS-CRP	Combined group（n=80）	95.67±12.54	24.38±4.65	32.990	P<0.001
	Control group（n=78）	93.92±13.38	32.67±6.42	42.010	P<0.001
	t	0.398	9.276	-	-
	P	0.849	P<0.001	-	-
IL-11	Combined group（n=80）	28.64±15.94	12.38±6.84	9.126	P<0.001
	Control group（n=78）	29.45±16.27	16.35±4.28	7.793	P<0.001
	t	0.316	4.361	-	-
	P	0.752	P<0.001	-	-
NLR	Combined group（n=80）	2.93±1.64	1.74±0.71	6.663	P<0.001
	Control group（n=78）	2.86±1.58	2.07±0.85	4.665	P<0.001
	t	0.273	2.651	-	-
	P	0.785	0.010	-	-

Table 5. **Comparison of Complications in two groups [n (%)]**

Complication	Combined group（n=80）	Control group（n=78）	χ2	P
Intracerebral infection	1（1.25）	5（6.41）	4.902	0.027
Pulmonary infection	0（0.00）	4（5.13）	4.209	0.040
Severe pain	6（7.50）	18（23.08）	7.439	0.006
Intracerebral rebleeding	0（0.00）	6（3.85）	6.397	0.011
Disturbance of water and electrolyte	5（6.25）	13（15.38）	4.006	0.045
Malnutrition	4（5.00）	10（12.82）	2.991	0.084

2.6 Prognosis

Prognosis of the two groups was evaluated according to the GOS grading standard. There exhibited no significant difference in the ratio of I to V between the two groups, but the excellent rate of GOS in the combined group was significantly higher than that in the control group (P<0.05). With GOS grade IV~V seen as good prognosis, the prognosis of patients with different clinical features was compared. The results showed that excellent rate of GOS showed a lower level in patients with hypertension history, age > 60, hematoma volume > 50 ml and GCS score ≤ 5 (P < 0.05). In order to further analyze the prognostic factors, with patient prognosis as dependent variable and the above factors as independent variables, and multiple factors analyzed using logistics, the result illustrated that patients with hypertension history, age > 60, hematoma volume > 50 ml and GCS score ≤ 5 after combined treatment were considered as independent risk factor(P < 0.05). See Table 6-8 for details.

Table 6. **Comparison of GOS score level in two groups**

Group	GOS score					
	Level Ⅰ	Level Ⅱ	Level Ⅲ	Level Ⅳ	Level Ⅴ	GOS excellence rate
Combined group（n=80）	2（2.50）	10（12.50）	25（31.25）	37（46.25）	6（7.50）	53.75（43/80）
Control group（n=78）	4（5.13）	16（20.51）	33（42.31）	21（26.92）	4（5.13）	32.05（25/78）
χ^2	0.747	1.844	2.078	6.349	0.375	4.289
P	0.388	0.174	0.149	2.520	0.540	0.038

Table 7. **Single-factor analysis of combined group**

clinical factors	Number of cases	Good prognosis (n=43)	Poor prognosis (n=37)	χ²	P
Age of years				4.606	0.032
＞60	31	12	19		
≤60	49	31	18		
Gender				2.235	0.135
Male	44	21	23		
Female	36	22	12		
Bleeding location				3.463	0.177
cortex	17	7	10		
basement	33	16	17		
others	30	20	10		
Hematoma volume （ml）				16.660	<0.001
＞50	25	5	20		
≤50	55	38	17		
GCS score （point）				40.280	<0.001
≤5	43	9	34		
＞5	37	34	3		
History of hypertension				4.483	<0.001
with	63	30	33		
without	17	13	4		

Table 8. **multiple-factor analysis of combined group using logistics**

clinical factors	regression coefficient	standard error	Wald	OR	95CI	P
Age of years (>60, ≤60)	2.206	0.932	5.601	9.082	（1.461-56.461）	0.018
Hematoma volume （＞50ml，≤50ml）	1.926	0.852	5.109	6.864	（1.292-36.475）	0.024
GCS score （≤5，＞5）	1.590	0.793	4.021	4.902	（1.037-23.188）	0.045
History of hypertension （with, without）	3.657	0.912	16.066	6.481	（6.481-231.722）	<0.001

3 Discussion

HICH occurs mostly in the bifurcation point of the basilar artery or the anterior, middle and posterior cerebral arteries. The break of elastic layer in the artery, atrophy of smooth muscle and cell degeneration would cause aggregation of platelet and fibrin hence lead to the functional changes of the brain, thalamus and cerebellum. The surgery is able to block the release of nerve products from the hematoma, thereby preventing the occurrence of edema around the hematoma, apoptotic necrosis, inflammatory cell infiltration, etc. [12]. Studies have demonstrated that using hemostasis in the early stage of intracerebral hemorrhage can effectively prevent the expansion of hematoma, furthermore, surgical intervention can eliminate blood clots, fully control blood pressure, alleviate secondary neurological damage, reduce patient mortality, and improve functional outcomes of HICH patients [13]. Although traditional craniotomy enjoys an excellent hematoma clearance rate[5], there has been a high proportion of severe or moderate disability in survivors after craniotomy [14], studies even have found out that craniotomy did not improve the patient's nerve function, but instead increased the formation of brain edema and brain tissue contusion[15]. In order to alleviate the damage of brain tissue and nerves caused by traditional surgery and reduce the incidence of postoperative rebleeding, the main focus of HICH research now remains to be how correctly carry out the administration of thrombolytic drugs and minimally invasive surgery [12].

By comparing combined treatment of HICH and urokinase perfusion with traditional craniotomy, it was demonstrated that the combination therapy features superior curative effect, which can significantly improve such perioperative indicators as intraoperative blood loss and operation time with a higher hematoma clearance rate and lower incidence of postoperative complications. In recent years, with the continuous advancement of medical technology and equipment, minimally invasive surgery has gained great popularity among patients and doctors. Among them, neuroendoscopy shows unique superiority in the treatment of intracerebral hemorrhage, which can not only fully expose and remove the intracranial hematoma using a small multi-angle rotating endoscope under good light, but also avoide damage to the surrounding blood vessels and brain tissue with less time of operation, amount of bleeding and occurrence of complication [16-17]. In addition, most elderly patients are generally less tolerant to craniotomy and brain contusion would occur after surgery [15. It is revealed by the study that neuroendoscopy for elderly patients with HICH or brain parenchymal injury can significantly improve the adverse outcomes, avoid tissue contusion caused by medical instruments, reduce brain edema, etc. [18]. On the other hand, urokinase is a widely used drug for intravenous thrombolysis with long treatment time window and low cost, which serves as an alternative of alteplase in acute ischemic stroke and acute cerebral embolism [19] . Secondly, studies have confirmed that urokinase can be used as a non-toxic plasminogen activator (PA) to wash the hematoma cavity, accelerate the dissolution of intracranial hematoma, shorten the drainage time and improve the edema around the hematoma for only local effects with high safety [20-21]. Finally, scholars as Sun have conducted a multi-center clinical treatment to analyze the efficacy of different HICH surgical treatments and postoperative indicators, and discovered that the mortality and incidence of rebleeding in patients decreased significantly after the combined treatment of HICH and urokinase perfusion [22]. These studies above have supported our findings from various aspects that the clinical value of combined treatment is obviously higher than that of conventional craniotomy, which deserves further investigation.

It is suggested by relevant study that systemic immune system would be activated and syndrome of systemic inflammatory response would occur among 20% of patients after intracerebral hemorrhage, which would seriously affect the prognosis of patients and increase the risk of dysfunction after discharge [23-24]. In this study, we observed the levels of serum hs-CRP, IL-11 and NLR in the two groups before and after treatment. The results showed that the levels of hs-CRP, IL-11 and NLR in the serum of the two groups both decreased after treatment, in which the combined group decreased more obviously than the control group. Inflammation is one of the main causes of secondary damage to intracerebral hemorrhage, which can lead to the destruction of the blood-brain barrier, directly or indirectly cause brain edema and death of brain parenchymal cell. Neutrophil is the earliest subtype of white blood cell occurred in infiltrative cerebral hemorrhage, which can produce reactive oxygen species and release pro-inflammatory proteases, increase the blood-brain barrier permeability, aggravate neuronal death, and even stimulate pro-inflammatory cytokines secreted by glial cells to further damage brain tissue after its apoptosis [23-24]. Wang and other scholars observed that the mortality rate of patients would increase with elevated NLR ratio after comparison of 224 HICH patients, which can predict the prognosis of HICH patients for 30 days [26]. On the other hand, elevated hs-CRP levels in patients with hemorrhagic stroke suggested occurrence of 07 inflammatory response in stroke patients, which may lead to severe neurological deficits and increase the risk of cerebrovascular events and death in patients [27-28]. Mario [29] and other scholars noticed that CRP, as an independent predictor of early hematoma growth in intracerebral hemorrhage and early neurological deterioration, seems to be able to reflect the degree of local blood-brain barrier damage and intracerebral hematoma formation. In addition, IL-11 may be involved in the pathological mechanism of intracerebral hemorrhage, and its level can reflect the severity of the HICH disease, which is related to the occurrence of hydrocephalus after intracerebral hemorrhage. Meanwhile, it can also serve as a predictor for nerve damage and death after intracerebral hemorrhage [30]. All of the above studies have shown that inflammation is an important therapeutic target for intracerebral hemorrhage, and NLR, hs-CRP and IL-11 may be involved in the development of intracerebral hemorrhage, which indirectly demonstrated that surgical treatment can improve clinical symptoms as well as inflammatory response of HICH patients, and combined therapy could exert better inhibitory effect on inflammatory response in HICH patients and bring about better prognosis.

Finally, we also compared the prognosis of patients underwent different treatments. The results showed that the excellent rate of GOS in the combined group was significantly higher than that in the control group, which was closely related to our previous findings that combination therapy can improve the patient's curative efficacy and improve hematoma clearance rate, reduce the incidence of complications and inflammatory reactions, reduce brain tissue contusion, thereby reducing the occurrence of adverse surgical outcomes. To further observe the patient's prognosis, we compared the relationship between prognosis and clinicopathological features of combined group. We determined that patients with elder age, hematoma volume >50 ml, history of hypertension, and GCS score ≤5 had a poor prognosis, which could be used as independent risk factors for combination therapy according to multi-factor regression analysis of Logistics. First of all, aging is an inevitable life process, and the gradual systemic function decline of cell, tissue, and various organs of the body can further lead to disease progression and death [31]. And the incidence of hypertension and the specific detection rate of cardiovascular diseases such as coronary heart disease and arteriosclerosis would also increase with aging [32]. Although older patients tend to be more tolerant to minimally invasive surgery than craniotomy [33], it is still undeniable that old age remains to be a risk factor for prognosis of HICH patients. In addition, HICH is very likely to cause white matter damage which may reflect the degree of pathological changes in the brain, and there is a clear relationship between the progress of white matter damage and the volume of cerebral hematoma, moreover, larger hematoma volume is more likely to cause more severe white matter damage, which would affect the long-term prognosis of patients[34-35]. Although An [36] and other scholars have shown that minimally invasive surgery is safer and more effective for HICH patients with a hematoma volume >50 mL than craniotomy, patients with larger cerebral hemorrhage may still have a higher risk of poor prognosis. GCS score is a method to evaluate the state of consciousness of patients. The lower the score, the more serious the consciousness disorder of patients would be, which can provide evaluation criteria for the state of consciousness of HICH patients[37-38], and the studies have shown that the admission GCS score of HICH patients was positively correlated with the GOS at 30 days after surgery, which both were important parameters reflecting the prognosis of patients[39]. A large number of studies have documented that hypertension is a risk factor for cerebral hemorrhage[40], the failure of timely regulation of hypertension may lead to rebleeding and poor prognosis of patients [41] , early active regulation of blood pressure can prevent further expansion of the hematoma and nerve's functional deterioration [42]. High risk, however, exhibited in the results of our study. Firstly, it may be related to the sample we have adopted, which basically meeted the diagnostic criteria for HICH while the proportion of newly diagnosed hypertension in this study was too small; Secondly, the sample size adopted in this research was too small, which would exert certain impact on the results of this study.

However, there still exists some deficiencies in this study. First of all, this study focused on the comparison of the efficacy and prognosis of HICH patients but failed to explore how hypertension induces cerebral hemorrhage, which requires further in-depth discussion and animal model establishment of other scholars from new perspectives. Secondly, as mentioned above, due to the experimental conditions and environmental limitations, the sample size adopted in this research was too small, which would exert certain impact on the results of this study, further multi-center clinical research is a necessity to reduce experimental errors.

In summary, combined treatment of MIEN and urokinase perfusion could exert a more preferable curative effect on HICH than conventional surgery, reduce the incidence of complications as well as inflammation, and improve surgical process and prognosis. And patients with hypertension history, age > 60, hematoma volume > 50 ml and GCS score ≤ 5 after combined treatment were considered as independent risk factor, which provided a new treatment for HICH patients and worth clinical promotion.

References

[1] Specogna A V, Turin T C, Patten S B, et al. Hospital treatment costs and length of stay associated with hypertension and multimorbidity after hemorrhagic stroke[J]. BMC neurology, 2017, 17(1): 158.

[2] An SJ, Kim TJ, Yoon BW. Epidemiology, Risk Factors, and Clinical Features of Intracerebral Hemorrhage: An Update. J Stroke. 2017;19(1):3–10. doi:10.5853/jos.2016.00864

[3] Sun Y, Xu B, Zhang Q. Nerve growth factor in combination with Oxiracetam in the treatment of Hypertensive Cerebral Hemorrhage. Pak J Med Sci. 2018;34(1):73–77. doi:10.12669/pjms.341.13395

[4] Feng Y, He J, Liu B, et al. Endoscope-assisted keyhole technique for hypertensive cerebral hemorrhage in elderly patients: a randomized controlled study in 184 patients[J]. Turk Neurosurg, 2016, 26(1): 84-89.

[5] Murthy J M K, Chowdary G V S, Murthy T, et al. Decompressive craniectomy with clot evacuation in large hemispheric hypertensive intracerebral hemorrhage[J]. Neurocritical care, 2005, 2(3): 258-262.

[6] Zhang J, Lu S, Wang S, Zhou N, Li G. Comparison and analysis of the efficacy and safety of minimally invasive surgery and craniotomy in

the treatment of hypertensive intracerebral hemorrhage. Pak J Med Sci. 2018;34(3):578–582. doi:10.12669/pjms.343.14625

[7] Tang Y, Yin F, Fu D, Gao X, Lv Z, Li X. Efficacy and safety of minimal invasive surgery treatment in hypertensive intracerebral hemorrhage: a systematic review and meta-analysis. BMC Neurol. 2018;18(1):136. Published 2018 Sep 3. doi:10.1186/s12883-018-1138-9

[8] Ye Z, Ai X, Hu X, et al. Comparison of neuroendoscopic surgery and craniotomy for supratentorial hypertensive intracerebral hemorrhage: A meta-analysis[J]. Medicine, 2017, 96(35).

[9] Chang Y H, Hwang S K. Frameless stereotactic aspiration for spontaneous intracerebral hemorrhage and subsequent fibrinolysis using urokinase[J]. Journal of cerebrovascular and endovascular neurosurgery, 2014, 16(1): 5-10.

[10] Wintermark M, Rizvi T. Principles of Clinical Diagnosis of Hemorrhagic Stroke[M]//Stroke Revisited: Hemorrhagic Stroke. Springer, Singapore, 2018: 109-132.

[11] Balestreri M, Czosnyka M, Chatfield D A, et al. Predictive value of Glasgow Coma Scale after brain trauma: change in trend over the past ten years[J]. Journal of Neurology, Neurosurgery & Psychiatry, 2004, 75(1): 161-162.

[12] Qureshi AI, Mendelow AD, Hanley DF. Intracerebral haemorrhage. Lancet. 2009;373(9675):1632–1644. doi:10.1016/S0140-6736(09)60371-8

[13] Rincon F, Mayer S A. Intracerebral hemorrhage: getting ready for effective treatments[J]. 。 Current opinion in neurology, 2010, 23(1): 59-64.gaoxuee

[14] Kolias A G, Kirkpatrick P J, Hutchinson P J. Decompressive craniectomy: past, present and future[J]. Nature Reviews Neurology, 2013, 9(7): 405.

[15] Szczygielski J, Mautes A E, Müller A, et al. Decompressive craniectomy increases brain lesion volume and exacerbates functional impairment in closed head injury in mice[J]. Journal of neurotrauma, 2016, 33(1): 122-131.

[16] Gui C, Gao Y, Hu D, et al. Neuroendoscopic minimally invasive surgery and small bone window craniotomy hematoma clearance in the treatment of hypertensive cerebral hemorrhage[J]. Pakistan Journal of Medical Sciences, 2019, 35(2).

[17] Qiu S, Liu T, Cao G, et al. Treatment of intracranial hemorrhage with neuroendoscopy guided by body surface projection[J]. Medicine, 2019, 98(19): e15503.

[18] Marklund N. Neuroendoscopy—a minimally invasive alternative in the surgical management of traumatic intracerebral contusions? [J]. Acta neurochirurgica, 2019, 161(2): 231-232.

[19] Zhang R, Wei H, Wu Y, et al. Outcomes and Treatment Complications of Intravenous Urokinase Thrombolysis in Acute Ischemic Stroke: A Retrospective Cohort Study[J]. Available at SSRN 3304297, 2018.

[20] Wen A Y, Wu B T, Xu X B, et al. Clinical study on the early application and ideal dosage of urokinase after surgery for hypertensive intracerebral hemorrhage[J]. Eur. Rev. Med. Pharmacol. Sci, 2018, 22: 4663-4668.

[21] Li Y, Yang R, Li Z, et al. Urokinase vs Tissue-Type Plasminogen activator for Thrombolytic evacuation of spontaneous intracerebral hemorrhage in Basal ganglia[J]. Frontiers in neurology, 2017, 8: 371.

[22] Sun H, Liu H, Li D, et al. An effective treatment for cerebral hemorrhage: minimally invasive craniopuncture combined with urokinase infusion therapy[J]. Neurological research, 2010, 32(4): 371-377.

[23] Tapia-Perez J H, Karagianis D, Zilke R, et al. Assessment of systemic cellular inflammatory response after spontaneous intracerebral hemorrhage[J]. Clinical neurology and neurosurgery, 2016, 150: 72-79.

[24] Boehme A K, Hays A N, Kicielinski K P, et al. Systemic inflammatory response syndrome and outcomes in intracerebral hemorrhage[J]. Neurocritical care, 2016, 25(1): 133-140.

[25] Ziai W C. Hematology and inflammatory signaling of intracerebral hemorrhage[J]. Stroke, 2013, 44(6_suppl_1): S74-S78.

[26] Wang F, Hu S, Ding Y, et al. Neutrophil-to-lymphocyte ratio and 30-day mortality in patients with acute intracerebral hemorrhage[J]. Journal of Stroke and Cerebrovascular Diseases, 2016, 25(1): 182-187.

[27] Gupta V, Gupta A K, Kakkar M, et al. Clinical evaluation of association between high sensitivity C-reactive protein and stroke[J]. International Journal of Advances in Medicine, 2016, 3(4): 820.

[28] LöPPönen P, Qian C, Tetri S, et al. Predictive value of C-reactive protein for the outcome after primary intracerebral hemorrhage[J]. Journal of neurosurgery, 2014, 121(6): 1374-1379.

[29] Mario Di Napoli M D, Parry-Jones A R, Smith C J, et al. C-Reactive Protein Predicts Hematoma Growth in Intracerebral Hemorrhage[J]. Stroke, 2014.

[30] Yang G, Shao G F. Elevated serum IL-11, TNF α,

and VEGF expressions contribute to the pathophysiology of hypertensive intracerebral hemorrhage (HICH)[J]. Neurological Sciences, 2016, 37(8): 1253-1259.

[31] Neki N S. Oxidative stress and aging[J]. Bangladesh Journal of Medical Science, 2015, 14(3): 221-227.

[32] Liu J, Ma J, Wang J, et al. Comorbidity Analysis According to Sex and Age in Hypertension Patients in China. Int J Med Sci. 2016;13(2):99–107. Published 2016 Jan 29. doi:10.7150/ijms.13456

[33] Tamura R, Kuroshima Y, Nakamura Y. Neuroendoscopic Removal of Acute Subdural Hematoma with Contusion: Advantages for Elderly Patients[J]. Case reports in neurological medicine, 2016, 2016.

[34] Zuo S, Pan P, Li Q, Chen Y, Feng H. White Matter Injury and Recovery after Hypertensive Intracerebral Hemorrhage. Biomed Res Int. 2017; 2017:6138424. doi:10.1155/2017/6138424

[35] Chen X, Chen Y, Xu M, et al. The Impact of Intracerebral Hemorrhage on the Progression of White Matter Hyperintensity[J]. Frontiers in human neuroscience, 2018, 12.

[36] An S J, Kim T J, Yoon B W. Epidemiology, risk factors, and clinical features of intracerebral hemorrhage: an update[J]. Journal of stroke, 2017, 19(1): 3.

[37] Reith F C M, Van den Brande R, Synnot A, et al. The reliability of the Glasgow Coma Scale: a systematic review[J]. Intensive care medicine, 2016, 42(1): 3-15.

[38] Mushtaq M, Khan Z, Afridi N M, et al. Predictive Value of Glasgow Coma Scale (GCS) Scores in Patients Presenting with Spontaneous Intracerebral Hemorrhage[J]. National Editorial Advisory Board, 2017, 28(10): 48.

[39] Islam M R, Khan M S K, Rahman M M, et al. Comparison of Glasgow Outcome Scale (GOS) and Glasgow Coma Scale (GCS) between Surgical and Conservative Management of Spontaneous Supratentorial Intracerebral Hemorrhage Patients: A Randomized Control Trial[J]. Journal of Current and Advance Medical Research, 2018, 5(2): 49-54.

[40] Ariesen M J, Claus S P, Rinkel G J E, et al. Risk factors for intracerebral hemorrhage in the general population: a systematic review[J]. Stroke, 2003, 34(8): 2060-2065.

[41] Morgenstern L B, Hemphill III J C, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association[J]. Stroke, 2010, 41(9): 2108-2129.

[42] Qureshi A I, Mohammad Y M, Yahia A M, et al. A prospective multicenter study to evaluate the feasibility and safety of aggressive antihypertensive treatment in patients with acute intracerebral hemorrhage[J]. Journal of intensive care medicine, 2005, 20(1): 34-42.