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Clinical efficacy and prognosis of aspirin combined with clopidogrel in patients with cerebral hemorrhage after operation

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Abstract. – OBJECTIVE: The aim of this study was to investigate clinical effect, the quality of life, and prognosis of patients with hy-pertensive cerebral hemorrhage treated with aspirin combined with clopidogrel after decompressive craniectomy and removal of intracranial hematoma.

PATIENTS AND METHODS: The individual patient data of 120 patients with hypertensive cerebral hemorrhage admitted to Affiliated Hospital of Jining Medical University from January 2015 to July 2016 were retrospectively analyz The patients were divided into a research g (62 cases) and a control group (58 cases). control group was treated with aspirin, while research group was treated with aspirin com bined with clopidogrel. The pre of ad verse reactions was compared twee he two groups. Activity of daily livin DL) w ed to evaluate the quality of life he toma before and after ation compared between the two gro The prog is of the two groups and the k rs of pos erative rebleeding in pat nts with bral hemorrhage were analyzed.

RESULTS: he pr valence adverse reactions in t rese group was significantly higher than the control group ($p<0.05$). The A sco of bot roups 14 days after the n w er than those before the opera n ($p<$), and the ADL scores he r h group were significantly lower th e control group 14 d after the ope n ($p<0.05$). The amount of hematoma in the groups after surgery was lower than that bef surgery ($p<0.05$), and the amount of hematoma in the research group was higher than that in the control group ($p<0.05$).

CONCLUSIONS: The combination of aspirin and clopidogrel will increase the prevalence of adverse reactions and reduce the quality of life of patients after decompressive craniectomy and removal of intracranial hematoma in patients with hypertensive intracerebral hemorrhage. Careful medication is required in clinic.

Key Words:

LDL oxidatio esa ians, S min, Episesamin, Platelet- ating fac ce drolase, Cardiovascular di

Introduction

ypertens cerebral hemorrhage is a mo neurosurgery and it is one of the common late stage complications in hypertensive nts[1]. Relevant reports[2] show that hypertensive intracerebral hemorrhage accounts for 93% of spontaneous intracranial hemorrhage. Intracerebral hemorrhage refers to the primary intracerebral parenchyma hemorrhage, which has a high incidence and is more common in people over 50 years old[3]. Vascular destruction is the fundamental cause of cerebral hemorrhage[4]. Relevant studies show that the annual incidence of hypertensive cerebral hemorrhage is (1-35)/100,000, accounting for 20%-30% of all stroke patients in Asia[5], and the 1-month mortality rate is 42%[6]. For the treatment of hypertensive intracerebral hemorrhage, decompressive craniectomy and removal of intracranial hematoma are commonly used in clinical practice[7].

Aspirin (acetylsalicylic acid) has become one of the most commonly used drugs because of its effect on analgesic, antipyretic, and prevention in cardiovascular disease[7,8]. The incidence of cardiovascular disease is relatively high in the elderly population; aspirin is often used by the elderly to prevent cardiovascular disease[9]. Nelson et al[10] made a research on disusing and taking aspirin before coronary artery surgery, suggesting that aspirin could inhibit platelet function and increases the risk of bleeding in patients undergoing coronary artery bypass grafting. Myles et al[11] studied the effect of aspirin on cardiovascular events and bleed-

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ing in healthy elderly people, and found that the use of low-dose aspirin as a primary prevention strategy in elderly people significantly increased the risk of hemorrhea. We hypothesized that aspirin could also increase the risk of bleeding in patients with intracerebral hemorrhage after decompressive craniectomy and removal of intracranial hematoma.

Clopidogrel is an irreversible p2y12 receptor antagonist[12]. It is a thienopyridine that irreversibly inhibits platelet aggregation by selectively binding ADP receptor of coupled adenylate cyclase on platelet surface[13]. It has been reported that dual antiplatelet therapy of aspirin and clopidogrel has been shown to reduce cardiovascular events in patients with acute coronary syndrome[14], meanwhile, some patients have also experienced drug-induced bleeding due to excessive platelet inhibition[15]. So, we would like to verify if aspirin combined with clopidogrel has lower or higher risk than aspirin alone in patients who undergo the operation of decompressive craniectomy and removal of intracranial hematoma.

Therefore, this study analyzed the effect of aspirin combined with clopidogrel on the rate of re-bleeding and quality of life in patients with hypertensive cerebral hemorrhage after decompressive craniectomy and removal of intracranial hema

Patients and Metho

General Data

A total of 120 cases of p wit sive cerebral hemorrhag mitt Affiliated Hospital of Jining Me Univers from January 2015 to July selected the research objects. P ents trea with aspirin were the control gr (58 cases), w 36 male cases, 22 female es, ag nging from 31 years old to 88 years averag e age (60.21±10.22). Patient trea with rin combined with clo were earch group (62 cases), 39 m e case female cases, age rang- fro old to 81 years old, average old (58 .02). This study have been approved by the E Committee of Affiliated Hospital of Jining M ical University and all the subjects have signed the informed consent.

Inclusion and Exclusion Criteria

Inclusion criteria: patients with a clear history of hypertension; patients diagnosed with cerebral hemorrhage; patients who have follow-up treatment in Affiliated Hospital of Jining Medical University after diagnosis; patients who can be able to cooperate with the investigation; patients without other serious organ diseases affecting this study; the informed consents were signed by the patients or their immediate relatives. Exclusion criteria: Patients with coagulation dysfunction and blood system diseases; patients with all kinds of non-hypertensive cerebral hemorrhage diseases; patients with hypersensitivity to clopidogrel, aspirin, or anticoagulant therapy; patients with advanced malignancy or dysfunction in blood, liver, or kidney.

Therapies

The standard large bone flap otomy wa er- formed under general anes sia, t matom was removed under micros e and the h was completely stopped bone f was re ved, and the drainage tube t cavity was routinely indwelt. The p t's p erativ al signs were monitored. e blood p was strictly controlled b een and 160 mHg. Symptomatic and supportive tre nt, including hemostasis, dehy prevention pilepsy, brain protection, a anti-infection were routinely given. The preop- ive contro oup took aspirin alone (purchased fr Shenyan Original Pharmacolabo Co., Ltd., SFD number: H20065051), 75 mg/d. The preoperative research group adopted the treatment opidogrel (purchased from Sanofi (Hangzhou) ha ceutical Co., Ltd, SFDA approval number: J20180029) combined with aspirin, with aspirin 75 mg/d, clopidogrel 100 mg/d.

Observational Indexes

The prevalence of adverse reactions was compared between the two groups. Activity of daily living (ADL) was used to evaluate the quality of life of the two groups of patients 14 days before surgery and after surgery. The full marks of activity of daily living (ADL) was 100. Patients whose scores <20 were classified as serious functional defects were regarded as not completely self-sufficient. Patients whose scores between 20 and 40 were regarded as "need great help", patients whose scores ranged from 40 to 60 were divided into "needed help", patients with scores of 60 were regarded as those with self-help ability. The higher the score, the higher the postoperative quality of life of patients. The amount of hematoma before and after surgery was compared between the two groups, and the amount of hematoma was calculated by the coniglobus formula = $7\pi/6 \times$ long axis $\times$ short axis $\times$ number of layers. All patients were followed up for 3 months with letters, phone calls, visits, and hospital reexaminations. The death of patients were regarded as cut-off events, and the

3-month prognosis survival curve was plotted to calculate the survival rate. The risk factors of postoperative rebleeding in patients with cerebral hemorrhage were analyzed[16].

Statistical Analysis

SPSS 24.0 statistical software (Beijing Strong-Vinda Information Technology Co., Ltd., Beijing, China) was used for statistical calculation of all experimental results, GraphPad8 (SOFTHEAD Inc., Shenzhen, China) was used for drawing and for checking the results twice. Enumeration data were all expressed in the form of (rate), and chi-square test was used for comparison between groups. Measurement data were all expressed in the form of mean±standard deviation. Repeated measurement analysis of variance was used for comparison between multiple time points, *t*-test was used for comparison between groups, Kaplan-Meier method was used for calculation of survival rate, and log-rank test was used for comparison of survival rate. $p<0.050$ was considered statistically significant. Univariate and multivariate logistic regression analysis were used to investigate the risk factors of postoperative rebleeding in patients with cerebral hemorrhage.

Results

Comparison of Clinical Da

There were no signifi t dif es be en the research group an control g erms of age, BMI, gende moki istory, ucation background, resi de n nality preoperative blood pressur eedi e, pr erative blood loss, ventri rupture, er general data ($p>0.05$) abl

Table I. Comparison of clinical data.

	Experimental group (n=62)	ontrol gr (n=58	*t* or χ^2	*p*
Age (years old)	58.69 02	0.21±10.22	0.777	0.439
BMI (kg/cm²)	15.84±1	15.92±1.23	0.362	0.718
Gender			0.009	0.925
Male	(62.90)	36 (62.07)		
Female	(37.10)	22 (37.93)		
Smoking			0.215	0.643
Yes	41 (66.13)	36 (62.07)		
No	21 (33.87)	22 (37.93)		
Education backgrou			0.259	0.611
<Senior high sc ol	36 (58.06)	31 (53.45)		
≥Senior high ol	26 (41.94)	27 (46.55)		
Residence			0.208	0.649
Cities	42 (67.74)	37 (63.79)		
Countrysi	20 (32.26)	21 (36.21)		
Nati			1.164	0.281
se	51 (82.26)	43 (74.14)		
Minori	11 (17.74)	15 (25.86)		
ope pressure (mmHg)				
pres	188.23±6.82	187.15±8.53	0.768	0.444
lic pressure	97.33±2.75	97.46±3.41	0.231	0.818
Bleedi rt			0.069	0.966
Basal g nglia	19 (30.65)	17 (29.31)		
Temporoparietal	20 (32.26)	20 (34.48)		
Parietooccipital	23 (37.09)	21 (36.21)		
Preoperative blood loss (n)			0.058	0.810
≤40 mL	35 (56.45)	34 (58.62)		
>40 mL	27 (43.55)	24 (41.38)		
Broken into ventricle (n)			0.005	0.944
Yes	21 (33.87)	20 (34.48)		
No	41 (66.13)	38 (65.52)		

Table II. Incidence of adverse reactions in the two groups of patients.

	Research group (n=62)	Control group (n=58)	χ^2	*p*
Rebleeding	15 (24.19)	6 (10.34)	3.981	0.046
Hydrocephalus	4 (6.45)	1 (1.72)	1.383	0.239
Infection	3 (4.84)	1 (1.72)	0.710	0.399
Adverse reactions rate	22 (35.48)	8 (13.78)	7.519	0.

Prevalence of Postoperative Adverse Reactions in the Two Groups

The prevalence of adverse reactions of the two groups was observed. The occurrence of adverse reactions in the research group was 35.48%, with 15 cases of postoperative bleeding, 4 cases of hydrocephalus, and 3 cases of infection. The occurrence of adverse reactions in the control group was 13.78%, with 6 cases of postoperative bleeding, 1 case of hydrocephalus, and 1 case of infection. The prevalence of adverse reactions in the research group was significantly higher than that in the control group ($p<0.05$) (Table II).

Comparison of ADL Scores in Patients of two Groups Before and 14 Days After Operation

There were no differences bet[illegible] scores in patients of two groups ($p>0$[illegible] ADL [illegible]ores 14 days after the operation of b[illegible]ups [illegible] er than that before the op[illegible]ion ([illegible]5), and the ADL scores 14 days aft[illegible] operation [illegible]atients in the research group w[illegible] sig[illegible]antly low[illegible]an that in the control gro[illegible] ($p<0.05$) [illegible]le III).

Comparison of Pre[illegible]erative and Postoperati[illegible] Hematomas B[illegible]n the two Gr[illegible]s

The am[illegible] of hema[illegible]eoperative and postoper[illegible]e [illegible]e two gr[illegible]ps were observed. There were no sig[illegible]ant differences between the tw[illegible]s preopera[illegible]ly ($p>0.05$). The amount o[illegible]ostoperative hematoma in the two groups was l[illegible]er than th[illegible]reoperative hematoma ($p<0.05$), a[illegible]the amo[illegible] of hematoma in the research grou[illegible]ier than that in the control group ($p<0.05$) (Table IV).

[illegible]val Results of the two Groups of Patients

By drawing the Kaplan-Meier survival curve, it was found that the 3-month survival rate of the patients in the research group was 80.65%, and the 3-month survival rate of the control group was 80.93%. There were no statistically significant differences in survival rates between the two groups ($p>0.05$) (Figure 1).

Table III. Co[illegible]ison preope[illegible]tive and 14 days postoperative ADL scores between the two groups.

	Preo[illegible]ative	Postoperative	*t*	*p*
[illegible]earch [illegible]up	[illegible]45±4.20	46.58±5.46	18.44	<0.001
[illegible]ntrol	29.63±4.43	64.56±5.71	36.81	<0.001
t	1.041	17.63		
p	0.300	<0.001		

Table IV. Comparison of preoperative and postoperative hematomas between the two groups (mL).

	Preoperative	Postoperative	*t*	*p*
Research group	57.40±9.81	51.64±8.15	3.556	<0.001
Control group	56.35±10.97	40.21±7.05	9.426	<0.001
t	0.553	8.191		
p	0.581	<0.001		

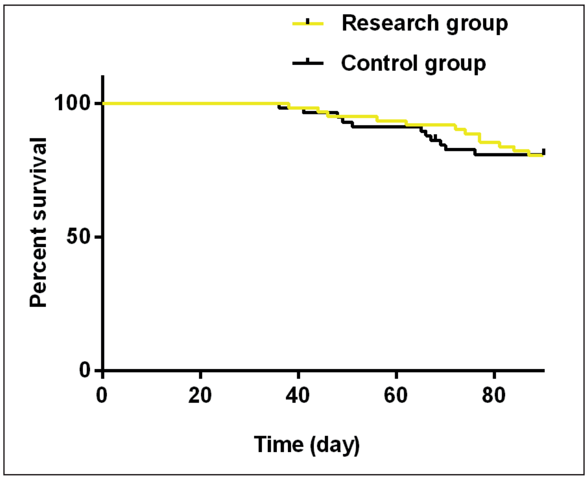

Figure 1. Survival results of the two groups of patients.

Univariate Analysis of Risk Factors in two Groups of Patients

There were statistically significant differences between the two groups of patients in terms of diabetes, drinking history and whether or not to take regular antihypertensive drugs (p<0.05). There were no statistically significant differences in age, body mass index (BMI), gender, smoking hi[illegible] education background, place of residence, na[illegible]ality, preoperative blood pressure, bleeding p[illegible] preoperative blood loss, extension [illegible] ventricle and other general data (p>0.05) (T[illegible]e

Multivariate Logistic Re[illegible]ion Analysis of Patients i[illegible]oth[illegible]ps

Differences existe[illegible] univaria[illegible]alysis of indicators (diabete[illegible]in[illegible] whethe[illegible] not to take regular an[illegible]ypertens[illegible]drugs) were assigned (assig[illegible]nt were sho[illegible] in Table VI). Then, SPSS [illegible]s use[illegible] choose LR: forward multivariate re[illegible]sio[illegible]nalysi[illegible] the results showed that di[illegible]tes w[illegible] inde[illegible]dent risk factor for cereb[illegible]rrhag[illegible]erative rebleeding (OR: 9[illegible]1, 95[illegible]CI: 1.4[illegible]62.809). Drinking alcohol [illegible]an i[illegible]nt risk factor for postoperative he[illegible]age (OR: 13.255, 95% CI: 2.175-80.895). Whet[illegible]r not to take regular antihypertensive drugs w[illegible]an independent risk factor affecting postoperative rebleeding of cerebral hemorrhage (OR: 22.775, 95% CI: 3.843-179.081) (Table VII).

Discussion

Hypertensive cerebral hemorrhage is a common disease treated by the department of neurosurgery. The incidence of cerebral hemorrhage in China is as high as 50.6 to 80.7 per 100,000 people, accounting for 18.8% to 47.6% of all acute cerebrovascular diseases[17]. This disease is a substantial cerebral hemorrhage that caused by the rupture of cerebral arterioles induced by hypertension, which is characterized by high fatality rate, high disability rate, quick onset, and severe condition[18]. Hypertensive intracerebral hemorrhage is c[illegible]d by the sudden rise of blood pressure o[illegible]f the original hypertensive disease. [illegible]r the for[illegible]ion of hematoma, the space occup[illegible] effect di[illegible]ly destroys the brain tissue [illegible]d ca[illegible] ischem[illegible] of surrounding tissues[19]. T[illegible] key to th[illegible]nt of cerebral hemorrhag[illegible] to eli[illegible]nate th[illegible]mass effect, to remove th[illegible]he[illegible]o[illegible] to red[illegible]e intracranial pressure, to [illegible]air da[illegible]ed ne[illegible]s, to prevent secondary [illegible]logical in[illegible] to promote the prognosi[illegible] so[illegible]s possib[illegible] Removal of intracranial hematoma [illegible] traditional surgical method fo[illegible]g hyperten[illegible]cerebral hemorrhage, and i[illegible]ffect has been widely recognized in clinic[21]. [illegible]et al[22] hav[illegible]hown that aspirin combined with cl[illegible]dogrel en[illegible]nces platelet activation and aggregat[illegible] [illegible]esearch of Zhou et al[23] on the effect of com[illegible]on of aspirin and clopidogrel therapy [illegible]rdiovascular outcomes, it was suggested that [illegible]gh the major cardiovascular events caused by combination therapy, such as myocardial infarction and stroke, were relatively reduced, it also resulted in a relative increase in hemorrhagic events. However, there are few reports on the effect of aspirin combined with clopidogrel on postoperative rebleeding rate of hypertensive cerebral hemorrhage. In this study, adverse reaction rate of the two groups were observed. There were 15 cases of postoperative rebleeding, 4 cases of hydrocephalus and 3 cases of infection in the research group, the prevalence of adverse reactions was 35.48%. There were 6 cases of postoperative rebleeding, 1 case of hydrocephalus, and 1 case of infection in the control group, and the incidence of adverse reactions was 13.78%. The occurrence of postoperative rebleeding in the research group was significantly higher than that in the control group (p<0.05), and the adverse reaction rate in the research group was significantly higher than that in the control group (p<0.05). In the research results of Zuo et al[24] on effectiveness and safety of dual antiplatelet therapy for Chinese intracranial and extracranial artery stenosis in ischemic cerebrovascular disease, although the aspirin combined with clopidogrel in prevention of stroke was better than aspirin alone, it caused much more bleeding than using aspirin

Table V. Univariate analysis in two groups of patients (n(%)) (x±SD).

	Research group (n=62)	Control group (n=58)	χ^2	*p*
Age (years old)	58.69±11.02	60.21±10.22	0.777	0.439
BMI (kg/cm²)	15.84±1.19	15.92±1.23	0.362	0.718
Gender			0.009	0.925
Male	39 (62.90)	36 (62.07)		
Female	23 (37.10)	22 (37.93)		
Smoking			0.[illegible]	0.[illegible]
Yes	41 (66.13)	36 (62.07)		
No	21 (33.87)	22 (37.93)		
Education background			0.25[illegible]	0.6[illegible]
<Senior high school	36 (58.06)	31 (53.45[illegible]		
≥Senior high school	26 (41.94)	27 (46[illegible]		
Place of residence			[illegible].208	0.649
Cities	42 (67.74)	[illegible].79)		
Countryside	20 (32.26)	(36.21)		
Nationality			[illegible]64	0.281
Han Chinese	51 (82.26)	43 [illegible]4)		
Minority	11 (17.74)	15 (2[illegible]		
Preoperative blood pres-sure (mmHg)				
Systolic pressure	188.23[illegible]32	187.15±8.53	0.768	0.444
Diastolic pressure	97.33[illegible]5	[illegible]46±3.41	0.231	0.818
Bleeding part			0.069	0.966
Basal ganglia	19 (30.6[illegible]	[illegible] (29.31)		
Temporoparietal	20 (32.26)	20 (34.48)		
Parietooccipital	[illegible].09)	21 (36.21)		
Preoperative blood loss (n)			0.058	0.810
≤40 mL	[illegible]6.45)	34 (58.62)		
>40 mL	[illegible] (43.55)	24 (41.38)		
Broken into ventricle (n)			0.005	0.944
Yes	[illegible](33.87)	20 (34.48)		
No	41 (66.13)	38 (65.52)		
History of diabetes mellitus			7.991	0.005
Yes	28 (45.16)	41 (70.69)		
No	34 (54.84)	17 (29.31)		
Alcohol abuse			12.010	<0.001
Yes	41 (66.13)	20 (34.48)		
No	21 (33.87)	38 (65.52)		
Whether o[illegible]e to tak[illegible]gular antihypertensive drugs				
Yes	22 (35.48)	37 (63.79)	9.609	0.002
No	40 (64.52)	21 (36.21)		

[illegible] In[illegible]in the study results of Johnston et [illegible]opidogrel combined with aspirin in the treatm[illegible]of acute ischemic stroke and high-risk transient[illegible]hemic attack, it was also suggested that the risk of massive bleeding was higher than that of patients receiving aspirin alone. According to the results of the two studies, the bleeding events caused by aspirin combined with clopidogrel were also higher than those caused by aspirin alone, which was consistent with our results. Hence, we concluded that the bleeding events caused by aspirin combined with clopidogrel were higher than those caused by aspirin alone. Preoperative and postoperative ADL scores of patients in the two groups were observed to estimate their quality of

Table VI. Assignment table.

Indexes	Assignment
Diabetes	Without=1; with=2
Drinking	Without=1; with=2
Whether or not to take regular antihypertensive drugs	Without=1; with=2

Table VII. Multivariate logistic regression analysis.

	B	SE	Wald	p	OR	95% CI
Diabetes mellitus	2.251	0.966	5.664	0.008	9.681	1.454-62.809
Drinking	2.589	0.942	7.838	0.005	13.255	2.175-80.895
Whether or not to take regular antihypertensive drugs	3.133	1.052	8.643	0.002	22.775	3.843-179.081

life, and there were no significant differences in preoperative ADL scores between the two groups ($p>0.05$). The ADL scores of both groups 14 d after the operation were higher than those before the operation ($p<0.05$), and the ADL scores of the research group were significantly lower than those of the control group 14 d after the operation ($p<0.05$), suggesting that both alone or in combination could improve patients' quality of life, but the effects in the control group were more significant. The preoperative and postoperative amount of hematoma of the two groups were observed. There were no significant differences preoperatively ($p>0.05$), the amount of hematoma in both groups were lower than those before the operation, and the research group was higher than the control group postoperatively. By drawing KM survival curve, it was found that 3-month survival rate of patients in the research group was 80.65%, and the rate in the control group was 80.93%. There were no statistically significant differences when the survival rates between groups were compared ($p>0.05$). By multivariate regression analysis, however, it was found that alcoholism, whether or not to take regular antihypertensive drugs were independent risk factors for postoperative rebleeding in patients with cerebral hemorrhage, suggesting that patients with cerebral hemorrhage should be paid more attention to clinical circumstance in the treatment. For patients with longer duration, more severe episodes, close attention needed to pay to the process of treatment.

Although the real-world postoperative bleeding rate of aspirin is lower than that of aspirin combined clopidogrel, we believe that it depends on patients' responsiveness to aspirin. Not all platelets may be inhibited when different patients take aspirin[26]. In addition, there are some limitations in this work. Firstly, the drug dose used in this study is single. Whether the postoperative bleeding rate of patients can be reduced by increasing or decreasing the drug dose is not further studied. Therefore, we hope to supplement our research results by observing the clinical efficacy of patients with different drug dosage regimens in future studies.

Conclusions

To sum up, the combination of aspirin and clopidogrel will increase the occurrence of adverse reactions and reduce the quality of life of patients after decompressive craniectomy and removal of intracranial hematoma in patients with hypertensive intracerebral hemorrhage. Careful medication required in clinic.

Conflict of Interest

The authors declare that they have no conflict of interest.

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