Use of antiplatelets

A survey of secondary prevention of ischemic stroke with intracranial hemorrhage history in Chinese patients

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ABSTRACT

الأهداف: دراسة ما إذا كان للعلاج بمضادات الصفائح الدموية أي تأثير على زيادة حالات النزيف داخل الجمجمة، وتقليص نسبة تكرر الجلطة الدماغية.

الطريقة: أُجريت هذه الدراسة الاسترجاعية في مستشفى بكين شويانغ، بكين، الصين، وشملت 256 مريضاً من أصل 336 مريض أتوا إلى المستشفى بعد إصابتهم بالجلطة الدماغية مع إصابة سابقة بنزيف داخل الجمجمة خلال الفترة من مايو 2005م إلى أكتوبر 2009م. لقد قمنا بتقسيم المرضى إلى مجموعتين: المجموعة التي أُعطيت مضادات الصفائح الدموية، والمجموعة التي لم تُعط هذا العلاج وذلك قبل إصابتهم بالجلطة الدماغية بمدة تتراوح ما بين 12–38 شهر. وقمنا باستخدام تحليل الانحدار اللوجستي من أجل تقييم مدى تأثير العلاج بمضادات الصفائح الدموية على نسبة تكرر الاحتشاء الدماغي والنزيف داخل الجمجمة.

النتائج: أشارت نتائج الدراسة إلى أن مضادات الصفائح الدموية لم تؤدي إلى زيادة نسبة تكرار النزيف داخل الجمجمة أثناء العلاج الوقائي من الجلطة (OR=1.431, CI: 0.198–2.467, p=0.577)، فيما كان ارتفاع ضغط الدم والنزيف الفصي من العوامل التي تزيد من خطر تكرر النزيف داخل الجمجمة. ولم يكن هناك اختلافاً واضحاً بين تكرر النزيف الفصي واستخدام مضادات الصفائح الدموية (x^2=0.516, p=0.468). ولقد قام العلاج بمضادات الدموية بتقليص حالات الإصابة بالاحتشاء الدماغي (OR=0.424, CI: 0.190–0.950, p=0.037).

خاتمة: أثبتت هذه الدراسة إمكانية استخدام مضادات الصفائح الدموية كعلاج وقائي ثانوي من الجلطة وذلك لدى المرضى المصابين سابقاً بنزيف داخل الجمجمة، مع عدم زيادة حالات الإصابة بالنزيف الدماغي. ونحن ننصح بالمحافظة على ضغط الدم في حدود المعدلات الطبيعية، مع عدم استخدام مضادات الصفائح الدموية عند الإصابة بالنزيف الصفي.

Objective: To explore whether antiplatelet (AP) agent therapy increased intracranial hemorrhage (ICH) incidence and reduced ischemic stroke recurrence.

Methods: A single-center retrospective cohort study involving 256 cases from 336 Chinese in-patients who had ischemic stroke with ICH history in Beijing Chaoyang Hospital, Beijing, China between May 2005 and October 2009 was conducted. Subjects were divided into 2 groups (with AP and without AP), followed by stroke events for 12-38 months. Logistic regression analysis was used to evaluate the effects of AP on cerebral infarction and ICH recurrence.

Results: The AP agent did not increase ICH recurrence in the secondary prevention of ischemic stroke with ICH history (odds ratio [OR] 1.431, confidence interval [CI] 0.198-2.467, p=0.577). Hypertension and lobar hemorrhage were risk factors of ICH recurrence. However, there was no statistical difference between recurrence of lobar hemorrhage and AP use (x^2=0.516, p=0.468). The AP agent significantly decreased the incidence of cerebral infarction (OR 0.424, CI 0.190-0.950, p=0.037).

Conclusion: The AP agents may be beneficial to secondary prevention of ischemic stroke with ICH history, with no increased incidence of cerebral hemorrhage. It would be safer to maintain blood pressure in the normal range and to exclude lobar hemorrhage when AP is used.

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Although the use of antiplatelets (AP) for the secondary prevention of ischemic stroke is proven, ischemic stroke with a history of cerebral hemorrhage was excluded from the indications by large-scale evidence-based clinical trials. There are many risk factors in common for hemorrhagic and ischemic stroke,[1] such as smoking, hypertension, and diabetes. Recurrent cerebral hemorrhage and/or infarction occurred in these patients. It was reported that there were no significant differences of one-year recurrence between cerebral hemorrhage and infarction in increased intracranial hemorrhage (ICH) patients.[2-4] Although AP may be beneficial to cerebral infarction recurrence, there was no protocol to follow for doctors in the secondary prevention of ischemic stroke in patients with ICH history. In a positive aspect, AP could prevent ischemic stroke recurrence, however, doctors were worried regarding ICH recurrence. We investigated and analyzed the status and outcome of AP in the secondary prevention of ischemic stroke in patients with ICH history.

Methods.

Patient selection and follow-up. A single-center retrospective cohort study involving 336 Chinese ischemic stroke in-patients with ICH history in Beijing Chaoyang Hospital, Beijing, China from May 2005 to October 2009 was conducted. All subjects were validated by cranial CT or MRI. Our hospital approved the study and all subjects gave informed consent. All patients were enrolled altogether and followed up for 12-38 months. Subjects aged between 41-80 years, diagnosed with ischemic stroke with a history of ICH were included. Patients with hemorrhage attributable to trauma, tumor, aneurysm, vascular malformation, and hemorrhagic conversion of arterial or venous infarction were excluded. Of these 336 patients, 80 cases were ineligible for the study (15 cases of cerebral hemorrhage secondary to cerebral vascular malformations and aneurysms; 5 cases of ischemic stroke secondary to hereditary diseases and vascular malformations). Eleven cases were followed up for less than 6 months due to death, 31 cases lost phone contact, and 18 cases denied access. Eventually, 256 patients or caregivers were visited by telephone or clinical service.

Data collection. Information collected from the time of admission included whether or not patients were referred from an outside hospital and initial findings. These included blood pressure, heart rate and rhythm, temperature, Glasgow Coma Scale (GCS) score, serum glucose level, and brain imaging characteristics, other accompanying risk factors (hypertension, diabetes, smoking, myocardial infarction [MI] and carotid angioplasty),[4] atrial fibrillation (AF) and coronary heart disease, management of the risk factors, family history and locations of ICH. All the data listed as follows were collected: duration of AP administration, recurrent neurological symptoms, and readmission. Recurrent ICH and cerebral infarction were confirmed by cranial CT or MRI. Based on initial imaging reports, ICH could be divided into lobar hemorrhage and infra-lobar hemorrhage by location. Lobar hemorrhage included hemorrhage of cerebral lobes and white matter below the lobes; infra-lobar hemorrhage included hemorrhage of basal ganglia, brain stem and cerebellum.[5]

Statistical analysis. A probability value of <0.05 was considered significant in the final model. Fisher exact test was performed to analyze the general categorical variables, unpaired t-test was applied to analyze continuous variables, and logistic regression analysis was used to evaluate the effects of AP on cerebral infarction and ICH recurrence. All statistical analyses used the Statistical Package for Social Sciences version 16 (SPSS Inc., Chicago, IL, USA).

Results.

Overall, 156 patients were not taking AP drugs, which include 5 cases who had bleeding-related side effects after taking AP drugs, and 10 cases who rejected AP drugs after taking them for less than 30 days. Eventually, recurrent ischemic stroke events and ICH comprised 38 cases and 23 cases. One hundred cases were taking AP drugs, including 88 cases on Aspirin (Bayaspirin enteric-coated, 100 mg, qd); and 12 cases on Clopidogrel (plavix, 75mg, qd). Sixty-nine subjects were treated with AP drugs without delay after ischemic stroke; patients with AF and MI were more compliable (**Table 1**). Subjects began taking AP at a later date (median 6.3 months after ICH). Nineteen cases with MI had been treated with coronary stent implantation, 6 in 34 cases with AF had been treated with warfarin. At the endpoint, recurrent ischemic stroke events comprised 15 subjects, and ICH 14 subjects. Overall, the stroke recurrence of the group had a lower trend (x^2=11.462, p=0.001) compared with recurrence of the non-AP group. It was found from the ICH baseline characteristics that hemorrhage usually occurred in the lobes of patients who were smoking (**Table 2**).

The incidence of cerebral hemorrhage was increased by AP in the secondary prevention of ischemic stroke with ICH history, but there was no statistical significance (odds ratio [OR] 1.431, 95% confidence interval [CI] 0.198-2.467, p=0.577). Poorly controlled high blood pressure and lobar hemorrhage were risk factors of ICH recurrence (**Table 3**). However, there was no statistical difference regarding recurrence of lobar hemorrhage between the 2 groups (x^2=0.516, p=0.468). The incidence of ischemic stroke recurrence was significantly reduced by the use of AP (OR 0.424, 95% CI 0.190-0.950, p=0.037), and diabetes was a risk factor related to ischemic stroke recurrence (**Table 4**).

Discussion. The evidence-based large-scale clinical trials showed that the incidence of cerebral hemorrhage was increased by AP use in ischemic stroke patients without cerebral hemorrhage history.[6,7] Recently, some retrospective studies with small samples showed that although the incidence of cerebral hemorrhage was increased, Aspirin was beneficial for patients with high risk factors of ischemic stroke with ICH history.[7,8] For ischemic stroke patients with ICH history, whether the AP drugs were used or not could be dependent upon the doctors according to clinical experience?

Our study analyzed the status of AP usage in ischemic stroke patients with ICH history, and the effects of AP on cerebral hemorrhage and infarction recurrence by prospective data analysis. There might be selection bias caused by the loss of contact or refusal of consent during the follow-up, but the baseline characteristics are consistent with the randomized control group.[9] It indicated that the probability of selection bias was minimal. This was shown that patients with MI and AF history were treated with AP when they visited the cardiologist. This may be because the cardiologists paid more attention to the incidence of ischemia recurrence after stenting, or they considered using AP to replace warfarin. This could also explain the trend of decreased cerebral infarction recurrence in patients with MI and AF; which may be related to AP administration. Lobar hemorrhage was independent upon diabetes mellitus, hypertension, AF, and smoking, however, increased significantly with age. Antiplatelet use did not significantly increase the incidence of cerebral hemorrhage in ischemic stroke patients with ICH

Table 1 - Characteristics of ischemic stroke patients with increased intracranial hemorrhage history treated with or without antiplatelets (AP).

Baseline characteristics	With AP (n=100) n (%)	Without AP (n=156) n (%)	t/x²	*P*-value
Male	68 (68)	95 (61)	1.329	0.287
Age (mean±SD)	61.74 ± 14.85	63.12 ± 13.91	3.378	0.453
Hypertension	74 (74)	108 (69)	3.378	0.181
Diabetes mellitus	52 (52)	77 (49)	1.583	0.444
Myocardial infarction	32 (32)	27 (17)	7.417	0.009
Coronary artery disease	51 (51)	84 (54)	0.198	0.701
Atrial fibrillation	25 (25)	7 (5)	23.443	0.000
History of smoking	50 (50)	70 (45)	0.644	0.443
History of alcohol	40 (40)	70 (45)	0.590	0.518
Lobe hemorrhage	15 (15)	15 (10)	1.708	0.233
LDL (mmol/L) (mean±SD)	2.94 ± 0.49	2.99 ± 0.26	1.025	0.307
INR (mean±SD)	1.53 ± 0.19	1.55 ± 0.13	0.976	0.331

LDL - Low density cholesterol, INR - International standardized ratio

Table 2 - Characteristics of patients with lobar and deep intracranial hemorrhage (ICH).

Baseline characteristics	Lobar ICH (n=30) n (%)	Deep ICH (n=226) n (%)	t/x²	*P*-value
Male	18 (55)	145 (64)	0.198	0.689
Age (mean±SD)	62.67 ± 11.48	62.57 ± 14.62	0.036	0.971
Hypertension	25 (83)	157 (69)	2.996	0.227
Diabetes mellitus	12 (40)	117 (52)	2.553	0.279
Myocardial infarction	7 (23)	52 (23)	0.002	0.968)
Ischemic heart disease	14 (47)	121 (54)	0.502	0.561
Atrial fibrillation	4 (13)	28 (12)	0.022	0.776
History of smoking	19 (63)	101 (45)	3.696	0.078
History of alcohol	11 (37)	99 (44)	0.551	0.557
Antiplatelet	15 (50)	141 (62)	1.708	0.233
LDL (mmol/L) (mean±SD)	2.94 ± 0.46	2.98 ± 0.35	0.381	0.706
INR (mean±SD)	1.56 ± 0.22	1.54 ± 0.14	0.522	0.605

LDL - Low density cholesterol, INR - International standardized ratio

Table 3 - Analysis of influencing factors of cerebral hemorrhage recurrence in ischemic stroke patients with intracranial hemorrhage history by logistic regression.

Variable	Odds ratio	(95% Confidence interval)	*P*-value
Gender	1.015	(0.973 - 1.059)	0.497
Age	2.020	(0.560 - 7.251)	0.281
Hypertension	7.291	(2.836 - 18.740)	0.000
Antiplatelet	1.431	(0.198 - 2.467)	0.577
Diabetes mellitus	1.134	(0.571 - 2.251)	0.720
Myocardial infarction	1.580	(0.442 - 5.648)	0.481
Coronary artery disease	1.853	(0.633 - 5.425)	0.260
Atrial fibrillation	0.663	(0.101 - 4.377)	0.670
History of smoking	1.669	(0.436 - 6.387)	0.454
History of alcohol	1.288	(0.371 - 4.465)	0.690
Lobe hemorrhage	128.289	(30.097 - 546.842)	0.000
LDL	0.332	(0.068 - 1.638)	0.176
INR	9.206	(0.221 - 384.258)	0.244

LDL - Low density cholesterol, INR - International standardized ratio

Table 4 - Influencing factors analysis of cerebral infarction recurrence in ischemic stroke patients with intracranial hemorrhage history by logistic regression.

Variable	Odds ratio	(95% Confidence interval)	*P*-value
Gender	0.952	(0.412 - 2.198)	0.908
Age	0.991	(0.968 - 1.015)	0.477
Hypertension	1.536	(0.952 - 2.478)	0.079
Antiplatelet	0.424	(0.190 - 0.950)	0.037
Diabetes mellitus	2.376	(1.503 - 3.756)	0.000
Myocardial infarction	0.763	(0.324 - 1.797)	0.536
Coronary artery disease	1.648	(0.827 - 3.285)	0.156
Atrial fibrillation	0.261	(0.050 - 1.369)	0.112
History of smoking	1.590	(0.613 - 4.127)	0.340
History of alcohol	0.612	(0.249 - 1.504)	0.284
LDL	3.284	(1.218 - 8.858)	0.019
INR	0.246	(0.021 - 2.940)	0.268

LDL - Low density cholesterol, INR - International standardized ratio

history. Hanger et al[10] confirmed this conclusion in the survey of AP usage in patients with cerebral hemorrhage. The experts in Japan[11] considered that AP agents were not independently associated with unfavorable outcome in lobar hemorrhage, however, they were a risk factor for cerebellar hemorrhage. It should be indicated that the use of AP did not follow the randomized control principles of clinical trials, which might underestimate the events of ICH recurrence because patients a with high risk of ICH recurrence avoided use of AP. However, it showed that the incidence of ICH recurrence was not increased by the taking of AP in ischemic stroke patients with ICH history. The major risk factors of ICH recurrence included location of cerebral hemorrhage and uncontrolled hypertension, and was also closely related to the outcome and turnover of the disease.[12] Our study also suggested that the lobar hemorrhage recurrence was not increased despite an increased trend of lobar hemorrhage recurrence by AP taking. The different pathogenesis of lobar and infra-lobar cerebral hemorrhage might be the reason. It has been demonstrated that lobar cerebral hemorrhage was closely related to amyloid vascular degeneration by neuropathology studies;[13-16] poorly controlled hypertension was another risk factor of ICH, and might be more closely related to infra-lobar hemorrhage.[17,18]

In conclusion, AP use significantly reduced the incidence of cerebral infarction recurrence in ischemic stroke patients with ICH history. These results provide evidence for the clinical use of AP. It was demonstrated by our study that AP use was beneficial to the secondary prevention of ischemic stroke in patients with ICH history, especially in those with risk factors of cardiovascular diseases, such as diabetes, AF, and MI. Considering that hemorrhage recurrence was more common in patients with poorly controlled hypertension and lobar hemorrhage, it would be safer if these patients were excluded when AP drugs were taken.[19,20] The more detailed advantages and disadvantages of AP use for secondary prevention of ischemic stroke patients with ICH history needs to be verified by further prospective randomized double-blind controlled trials.

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