

Retrospective Study on the Safety and Efficacy of Clopidogrel in the Treatment of Acute Cerebral Infarction

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Abstract: Till now there's no large sample, randomized and double-blinded research of clopidogrel in acute cerebral infarction. There have been some studies of combined and loading dosage of clopidogrel for antiplatelet treatment but the NIHSS is no more than 5 points. Our study is to evaluate the efficacy and safety of clopidogrel in acute ischemic stroke. It's a single center retrospective study. Collect information of patients with acute ischemic stroke from January 1st 2012 to May 31st 2015, using of different antiplatelet drugs, occurring of progressive ischemic stroke, risk factors of cardiovascular and cerebrovascular diseases, etiological classification of cerebral infarction, NIHSS scores on admission and 7 days after admission were collected and was classified into different groups (NIHSS \leq 3, 4-7, 8-15 and $>$ 15 points). correlation statistical analysis was performed with chi-square test. A total of 1008 patients were collected, 94 of them had progressive ischemic stroke. There was no significant difference between aspirin group and clopidogrel group (routine clopidogrel group and loading clopidogrel group) within 7 days of onset. Clopidogrel group was superior to aspirin in reducing early recurrence and deterioration within 24 hours while NIHSS on admission was greater than 3 points. PIS has close relation to admission time after onset and severity of clinic. There was no significant difference in the incidence of safety events between aspirin and clopidogrel (routine clopidogrel and loading clopidogrel). Loading dosage of clopidogrel is as safe as the routine group and aspirin group.

Keywords: Acute Cerebral Infarction, Clopidogrel, Progressive Ischemic Stroke, Cerebral Infarction Hemorrhage Transformation

1. Introduction

Although early time using of aspirin for antiplatelet therapy can reduce stroke recurrence, but the net benefit of aspirin is relatively low and is useless for progressive ischemic stroke [1, 2]. Clopidogrel can provide an additional of 8.7% reduction than aspirin in relative risk [3]. A number of antiplatelet drug studies for patients with acute cerebral infarction such as CHANCE [4], SUMMPRIS [5], SOCRATES [6] and CLASS-CHINA [7] had shown exploration and bright prospect of combined and loading dosage of clopidogrel for antiplatelet treatment. LOAD [8] had proved the safety of loading dosage of clopidogrel and aspirin. In the research of SOCRATES [6], Most of the patients with middle cerebral

infarction were mild stroke patients (NIHSS score \leq 5 points), in which the CHANCE study [9] answered the TIA (ABCD2 score \geq 4 points) and the minor stroke (NIHSS score \leq 3 points), the superiority of combined and loading dosage of antiplatelet over aspirin alone.

The superiority of clopidogrel over aspirin was not clear in patients of NIHSS with 4-7 points and lack of related clinical research which worth clinical studying. Our center start to use clopidogrel from 2005 and standard operating procedures (SOP) from 2012 require loading dosage of clopidogrel and combination with aspirin for 7 days in patients of NIHSS score of \leq 7 points. Patients with intracerebral infarction were treated with loading dosage of clopidogrel. The aim is to evaluate whether clopidogrel is superior to aspirin and whether loading dosage of clopidogrel is superior to aspirin.

2. Methods

2.1. Design Overview

This study was based on a single center and retrospective study. All cases were from the Department of Neurology of the first affiliated Hospital of Jinan University. Patients with acute ischemic stroke admitted to hospital within 7 days of onset from January 1st 2012 to May 31st 2015 were collected.

2.2. Participants

Over 18 years of age; The diagnosis of cerebral infarction in patients with acute cerebral infarction within 7 days of onset was in accordance with the diagnostic criteria of cerebral infarction in the National guidelines for the Prevention and treatment of Cerebrovascular Disease in 2014 [10] and was confirmed by CT / MRI. Subjects were excluded if they underwent emergency thrombolytic therapy or intravascular therapy; Patients who received anticoagulant drugs within 7 days of admission included low molecular weight heparin (LMWH); Patients with asymptomatic cerebral infarction were found after admission; Patients enrolled in clinical studies; Patients who developed from transient ischemic attack to cerebral infarction after admission; Patients with previous cerebral infarction were treated with antiplatelet drugs in the recent 2 weeks.

2.3. Methods of Data Collection

The electronic medical records included "cerebral infarction", "atherosclerotic cerebral infarction", "cardiogenic cerebral embolism", "lacunar infarction" and "cerebrovascular disease" according to the diagnosis of discharge from January 1st 2012 to May 31st 2015. Screen admission and discharge departments one by one, check each electronic case to register the course of hospitalization and related clinical data, and cross-check, modify and supplement the variable data.

NIHSS score ≤ 7 points: loading dose of clopidogrel 300 mg (75mg qd from the next day) and aspirin 100mg QD; determined according to specific circumstances. If the patient has previous gastric hemorrhage and other intolerant double antibodies a history of cerebral infarction, coronary heart disease, They were given aspirin 100mg/d temporarily, clopidogrel 75mg/d from the second day, and Clopidogrel / aspirin was given according to ESSEN score after 7 days.

NIHSS score ≥ 8 points, according to the ESSEN score, clopidogrel (first time of 300mg loading dose and then 75mg QD) or aspirin 100mg QD was given.

2.4. Collection of Clinical Data

Sex, age of patients with BMI, demographic data of smoking and drinking history. The time from onset to admission. NIHSS, mRS and BI scores of admission and after treatment of 7d, images of patients admitted to hospital without bleeding transformation, such as hemorrhagic transformation of ECASSII. Record the bleeding in patients with bleeding type conversion and location of infarction.

Past medical history, such as hypertension, diabetes,

coronary heart disease, atrial fibrillation, valvular heart disease, stroke (cerebral hemorrhage or cerebral infarction).

Pre-hospital medication: antiplatelet drugs (clopidogrel or aspirin) were excluded, anticoagulants (Dabigavin, warfarin, rivastatin, statins) were excluded.

Choice of antiplatelet and Lipid-lowering drugs after admission.

Factors influencing the recurrence or progression of cerebral infarction and the transformation of cerebral infarction hemorrhage: blood pressure at admission, fasting blood glucose, CRP, low density lipoprotein, INR, whether platelets are less than $200 \times 10^9/L$, whether there is fever within 7 days of admission, whether the condition of consciousness disorder at admission is a large area of cerebral infarction.

2.5. Interpretation of Observation Indicators

Smoking history, drinking history and past medical history, according to the records of the case.

After admission, hyperlipidemia was detected, and hyperlipidemia was defined as: total cholesterol $> 5.18 \text{ mmol/L}$, triglyceride $> 1.70 \text{ mmol/L}$, low density lipoprotein $> 3.37 \text{ mmol/L}$.

Large area cerebral infarction: the Chinese guidelines for the Prevention and treatment of Cerebrovascular Disease in 2014 defined as more than one lobe with a diameter of more than 5 cm [10].

2.6. Therapeutic Endpoint Events

2.6.1. Main Outcome Endpoint Events

Early recurrence or progression: NIHSS scores after admission to 7 d were higher than baseline ≥ 2 points.

2.6.2. Secondary Therapeutic Endpoint Events

New Clinical Vascular events: recurrence of Ischemic Stroke (excluding TIA), Myocardial Infarction, Pulmonary Infarction, Deep Venous Thrombosis, other macrovascular events, Vascular death: death due to stroke (ischemic or hemorrhagic, systemic hemorrhage, myocardial infarction, pulmonary embolism, congestive heart failure, sudden death, or arrhythmia). Adverse reactions / severe adverse reactions.

2.7. Safety Endpoint Events

2.7.1. Main Safety Endpoint Events

Life-threatening hemorrhage: symptomatic intracranial hemorrhage or severe extracranial hemorrhage (hemoglobin reduction $\geq 50 \text{ g/L}$);

Hemorrhagic shock; or need blood transfusion ≥ 4 units of RBC or equivalent volume of whole blood.

2.7.2. Minor Security Endpoint Events

Moderate haemorrhage: GUSTO study [9] defines (with persistent haemorrhage sequelae, or intraocular hemorrhage leading to severe loss of vision; or requiring a transfusion of 2-3 units of RBC or equivalent volume of whole blood; small bleeding events, Refers to bleeding events that do not require blood transfusion or do not cause hemodynamic changes, such

as small bleeding spots in the skin, positive occult blood in stool, etc.

2.8. Statistical Methods

Statistical Analysis of data by SPSS19.0 Software. Compare the early recurrence or progression of patients which clopidogrel (routine and loading dosage) or aspirin for 7d. Measurement data adoption by chi-square test, The counting data is expressed by rate or median, All tests are bilateral hypothesis tests, inspection level $\alpha=0.05$.

3. Results

3.1. General Information

From January 1st 2012 to May 31st 2015, a total of 1008

cases were recorded. Among them, 94 cases suffered from early recurrence or progression of major end point events (progressive ischemic stroke, PIS), 8 cases died, and 4 cases of secondary end point events occurred. The test efficiency of the statistical analysis was obviously reduced, so only the statistical analysis of the main curative effect events was carried out. Among them, 2 cases were the main safety endpoint events, 38 cases were secondary safety events. The total end point events were 40 cases. There were 668 males and 340 females, 325 patients with a personal history of smoking, 91 patients with a personal history of drinking, 42 patients with massive infarction, 80 patients with disturbance of consciousness at admission. There were 55 cases of somnolence and 25 cases of coma (the general information features see Table 1).

Table 1. The general information.

Parameter	Effective number	minimum value	Maximum value	Average value
Age	1008	20	96	65.02
BMI	606	.00	41.67	23.54
NIHSS on admission	1008	0	27	5.00
mRS on admission	1007	0	5	2.69
SBP on admission	1002	13	248	154.32
DBP on admission	1001	5	887	86.28
Fasting plasma glucose	989	1.00	44.500	7.32
INR	940	.76	11.1	1.21
H-CRP	858	.00	244.36	12.52
LDL-C	990	.52	18.30	3.05
NIHSS at 7 th day or discharge	1000	0	27	4.08
mRS at 7th day or discharge	1000	0	5	2.19

The total number of patients with clopidogrel was 876(86.9%). There were 132 cases (13%) in aspirin group, 163 cases (16%) in routine clopidogrel group and 205 cases (20%) in loading clopidogrel group. The total number of aspirin and clopidogrel alone using patients was 500, which was the main object of this data analysis (see figure 1).

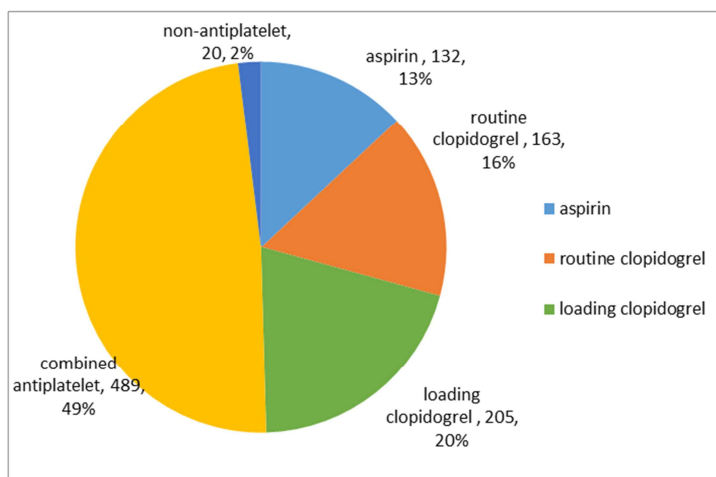


Figure 1. Antiplatelet groups.

3.2. PIS with Relation to Onset to Hospitalization Time and NIHSS

Table 2. PIS within or after 24 hours after onset of clinic.

Group	Cases with PIS	Cases without PIS	Total	P
Admission within 24 hours	69(13.7%)	434	503	<0.001
Admission after 24 hours	25(4.95%)	480	505	
Total	94	914	1008	

This table shows that the percentage of progressive ischemic stroke is 13.7% in the patients within 24 hours from onset to hospitalization and means that over 70% of the progressive ischemic stroke occurs within the first 24 hours or the first days from onset. The P value is less than 0.001 and means PIS has clear relation to Onset to hospitalization time.

The severity of clinc is classified in groups of NIHSS of 0-3 and over 3 points. There's 233 cases in the 0-3 group and with 19 cases (8.15%) of PIS but without statistical difference among the aspirin and clopidogrel groups (routine and loading dose).

3.3. PIS with Relation to Different Antiplatelet Groups Within 24 Hours After Onset

Table 3. PIS between clopidogrel and aspirin groups within 24 hours after onset.

Antiplatelet program	Aspirin	Routine clopidogrel	Loading clopidogrel
Without PIS	39	66	83
With PIS (%)	19(32.75%)	11(14.28%)	12(12.63%)
P	0.045	0.057	0.021
Total	58	77	95

This table shows that PIS is much higher in aspirin group than the routine and loading clopidogrel groups in patients within 24 hours from onset to hospitalization (32.75% vs 14.28% and 12.63%).

Table 4. PIS among different antiplatelet groups NIHSS>3 points.

Antiplatelet program	Aspirin	Routine Clopidogrel	Loading Clopidogrel
Without PIS	18	40	53
With PIS (%)	12(66.67%)	10(20.00%)	8(13.11%)
Total	30	50	61

This table shows that in the patients of NIHSS over 3 points, PIS is much higher in the group of aspirin while the clopidogrel group is much lower (66.67% vs 20.0% and 13.11%).

Table 5. PIS among different groups of NIHSS>3 points.

NIHSS Group	With PIS (%)	Without PIS	Total
NIHSS 4-7	26(16.56%)	131	157
NIHSS 8-15	16(26.23%)	45	61
NIHSS >15	7(20.0%)	28	35
Total	49(19.37%)	204	253

This table shows that the PIS of NIHSS within 7 points is lower than those over 7 points. The average PIS percentage is 19.37% in patients of NIHSS over 3 points which is much higher than those within 3 points (8.15%).

3.4. Safety Endpoint Event

Major Safe end event: 2cases. Both were Symptomatic intracranial hemorrhage of NIHSS increasing over 4 points and underwent aspirin and clopidogrel respectively.

Table 6. Secondary Safe end event among different antiplatelet groups.

Antiplatelet program	Aspirin	Routine Clopidogrel	Loading Clopidogrel
No safe end	125	191	156
Secondary safe end event (N, %)	7(5.3%)	14(6.83%)	6(3.68%)
P	-	0.572	0.534
Total	132	205	163

This table shows that there's no obvious difference between aspirin and Clopidogrel groups in safe endpoint events.

4. Discussion

This is a retrospective study and the range of information is restricted in 7 days. The average of early recurrence or progression percentage is 9.33% when compared with other researches such as the CLASS-CHINA [7]in which the PIS in loading dosage group is 16.1% and the control group is 14.9%. It may because of the lack of case recorded and short of studying time. Loading dosage of clopidogrel can rapidly achievement homeostasis state of drug and has been proved to be safe [11, 12].

PIS is most likely to occur in the patients within 24 hours from onset to hospitalization which prompt the first 24 hours is the most important for ischemic stroke patients. Although the PIS may be affected by multiple factors, time is always the most important. The sooner of treatment started, the fewer of PIS. But there's no recorded data of the time from onset or treatment to PIS and this need for further work and research. The criteria from onset to progression of time is not so clear and can range from 2 to 30 hours or even 7 days [13].

The PIS percentage is only 8.15% in patients of NIHSS within 3 points while the average PIS percentage is 19.37% in patients of NIHSS over 3 points which prompt the more severe of neurological deficit, the higher of PIS percentage. This may because of higher risk stratification of patients with higher NIHSS scores.

CHANCE study [1] proved the superiority of loading and combination of antiplatelet over aspirin alone in TIA (ABCD2 score ≥ 4 points) and the infarction (NIHSS score ≤ 3 points) patients. In our study there's no superiority of clopidogrel to aspirin in patients of NIHSS score ≤ 3 points. Whether there'll be superiority of loading and combination of clopidogrel and aspirin to aspirin with different TOAST etiology of stroke for over 7days or even 21 days need for further research.

Combined antiplatelet group stands for 54.7% (269/492) in patients of NIHSS 0-3 points and 56.6% (454/802) in patients of NIHSS 0-7 points. There's a total of 489 cases (49%) with combined antiplatelet treatment which means the standard operation process is insufficient and part of the patients with higher than 7 points of NIHSS underwent antiplatelet drug of more than one kind.

There's no obvious difference between aspirin and clopidogrel groups in safe endpoint events which prompt that loading dosage of clopidogrel is also safe in clinc and the PRESS-CHINA and CLASS-CHINA have proved the safety

of loading clopidogrel.

5. Conclusion

Clopidogrel group was superior to aspirin in reducing early recurrence and deterioration within 24 hours, while NIHSS on admission was greater than 3 points and NIHSS score was 8-15.

PIS has close relation to admission time after onset of clinc especially the first 24 hours is the most important for ischemic stroke patients which prompt once again time is brain. Clopidogrel is superior to aspirin in patients within 24 hours from onset to hospitalization. Besides, PIS has close relation to severity of clinc and the PIS in patints of NIHSS within 3 points is much lower than those over 3 points. In the patients of NIHSS over 3 points the clopidogrel group is superior to aspirin group.

There's no obvious difference between aspirin and clopidogrel groups in safe endpoint events and loading dosage of clopidogrel is as safe as the routine group and aspirin group.

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