Clinical Research

Feasibility of intravenous administration of aspirin in acute coronary syndrome

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Objectives To compare the clinical effects of intravenously and orally administered aspirin in the treatment for acute coronary syndrome (ACS), and to evaluate the adverse effects of intravenous administration of aspirin.

Methods One hundred and twenty-five patients with unstable angina pectoris or acute myocardial infarction were randomized into three groups: group 1 received intravenous aspirin (300mg/d, n =40), while groups 2 (n =42) and 3 (n =43) received orally administered aspirin (100mg/d and 300mg/d, respectively). The control group included 30 patients with no heart disease or blood disease, and they had never taken aspirin and clopidogrel. Blood samples were taken at 2nd and 7th day of hospitalization. Platelet aggregation and the level of platelet activation marker CD62p were measured and compared among the groups. Patients were followed up for 6 months for the occurrence of major adverse cardiovascular events.

Results There were no statistically significant differences in the decrease in adenosine diphosphate (ADP)-induced platelet aggregation rate (12.01±10.45%, 6.76±14.62% and 9.73±16.72% for group 1, group 2 and group 3, respectively), the decrease in arachidonic acid (AA)-induced platelet aggregation rate (6.73±11.34%, 6.95±12.45% and 7.57±13.11%, respectively), and the decrease in CD62p level (10.89±18.62%, 8.92±11.57% and 7.05±15.67%, respectively). At six months, there were 4 deaths (10%) in group 1, 4 deaths (9.5%) in group 2 and 5 deaths (11.6%) in group 3 (P >0.05).

Conclusions Intravenous administration of aspirin provides a new approach as an anti-platelet treatment for ACS patients, especially those who can not tolerate oral administration of aspirin. (J Geriatr Cardiol 2008; 5:212-216)

Key words Coronary disease; aspirin; injection, intravenous

Previous investigations indicated that acute coronary events (acute myocardial infarction, unstable heart-stroke and sudden cardiac death) were related to disruption of atherosclerotic plaques, platelet activation and thrombogenesis. The expert agreement in China (2005) pointed out the clinical applications of aspirin in atherosclerotic cardiovascular diseases: patients that suffered from acute coronary syndrome were recommended to receive combined treatment with oral administration of aspirin and clopidogrel no matter whether the ST sections of them were elevated; they should be administered with a loading dose of 150-300mg under the clinical circumstances that immediate anti-thrombus therapeutic effects are needed (such as acute coronary syndrome or acute ischemic apoplexy) to ensure rapidly and completely inhibit thromboxane A2 dependent platelet aggregation; it is recommended that the dosage for long-term use should be 100mg/d (75-150mg/d). But some patients can not take aspirin orally due to diseases of digestive tract and other reasons, could they be administered intravenously? This investigation observed the therapeutic effects and safety of intravenous administration by drug administration from intravenous route for ACS patients in the acute stage, and the results were compared with those of the oral administration group, and the clinical efficicencies within six months were also observed at the same time.

Data and methods

Subjects

Inclusion criteria: patients that were hospitalized in the Department of Cardiology, Fuxing Hospital Affiliated to Capital University Medical Sciences from April 2006 to February 2007 were included, and they have been approved by the Ethics Committee and agreed to take part in this clinical investigation. One hundred and twenty-five cases of unstable angina or acute myocardial infarction patients that were confirmed by coronary angiography to meet the diagnostic criteria of ACS from WHO were included, aged 43 to 90 years old, and had orally taken 100mg/day aspirin for at least one week before hospitalization. Exclusion criteria: aspirin hypersensitiveness, asthma; various kinds of blood diseases, hematologic diseases, or hemorrhagic tendency; definite reactive and peptic ulcer at present; blood platelets count >450 000 or <100 000; non-steroidal anti-inflammatory drugs were used within the past four weeks.

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**Grouping and drug administration**

All the patients that suffered from acute coronary syndrome were immediately administered with 300mg aspirin and a loading dose of 300mg clopidogrel after their hospitalization, and then they were grouped and subjected to treatment according to the randomized block design:

1. Group 1: Patients received intravenous aspirin (300mg/d); [it was equal to intravenous administration with 540mg/d (Aspisol) within 10min]
2. Group 2: Patients received oral aspirin (100mg/d)
3. Group 3: Patients received oral aspirin (300mg/d)
4. Control group: Patients that had no organic heart disease and blood disease as well as those had never taken aspirin or clopidogrel.

No statistical difference was found in the three groups of basic drugs including β- receptor blocking agent, ACE or ARB group, statins, Ca²⁺ antagonists and low molecular heparin group. They were changed into oral administration with 100mg/d aspirin after one week, and the patient can be administered for long term if no contradiction was found. All of the included ACS patients kept on taking clopidogrel orally for over one week, and those not subjected to stenting operation can be administered with this drug according to the practical situations, and patients that were subjected to interventional therapy can take this drug for 9-12 months or even longer according to the actual situations.

**Laboratory examinations**

Patients in three groups were subjected to blood collection on empty stomach in the morning at the 2nd and 7th day after hospitalization (the first blood collection after the hospitalization was considered as a drug administration), and the items in the examinations included platelet aggregation, the level of platelet activation marker CD62p and other conventional examinations such as blood routine and the items in the examinations included platelet aggregation, the level of platelet activation marker CD62p and other conventional examinations such as blood routine.

**Major reagents**

The reagents ADP and arachidonic acid (AA) were provided by Cayman Co. and Sigma Co., USA; CD62p antibody: the IgG1 antibody in rat was provided by BD Co. of USA; intravenous aspirin (0.9g Aspisol equaled to 0.5g aspirin) was produced by Anhui Fengyuan Pharmaceutical Group, National Production Permission Number: H34022437; oral aspirin: Bayer Pharmaceutical and Healthcare Co. Germany.

The determination of adenosine diphosphate (10μmol/LADP) and adenosine diphosphate (0.5mg/mLAA) induced platelet aggregation rates: 2.7 mL blood was collected (1:9 anticoagulation) and then transferred to a vacuum collecting tube containing 0.3 mL 3.18% natrium citricum. The platelet-rich plasma (PRP) was extracted when the solution was gently and fully mixed and centrifuged at 1000r/min for 10min, and the remaining blood was centrifuged at 3 000r/min for 30min, then the platelet poor plasma (PPP) was taken out. The blood platelets count of PPP was (10-20)×10⁹/L; PPP was used to adjust the PRP to (200-300)×10⁹/L; 200ml PRP and 200ml PPP were added to two tubes for comparative tests, respectively, and the transmittances of PRP and PPP were adjusted into 90 and 10 in the platelet aggregation device; a stirrer bar was added to the PRP, then the tubes for comparative tests were kept at 37℃ for 3min; 10μmol/L ADP and 0.5mg/ml AA inductor in 1/10 of the volume were added to the PRP after the solution was stirred for 10-20s, and the time for aggregation recording should be no less than 3min. Notice: the sequence in the blood collection was the second tube, and the mixing should be gentle and the entire determination should be finished within 3h.

**The determination of platelet activation marker CD62p**

Vacuum blood taking needles were used to puncture the vein, and 2 mL blood was collected in the second natrium citricum anticoagulant tube, and 5 mL whole blood was added immediately to the plastic determination tube containing 10ml IgG1 antibody from rat; then they were gently mixed and immediately subjected to reaction at room temperature in dark for 20min; 1 mL PBS fixative solution containing 1 mL 1% paraformaldehyde was added for fixation for 20 min in each tube after the time for reaction was sufficient, and the tubes were stored in a refrigerator of 4℃ before determined within 24h; the determination was carried out by using a flow cytometer. (The Hematological Laboratory Fuxing Hospital Affiliated to Capital University Medical Sciences). Notice: the sequence in the blood collection was the second tube, and the mixing should be gentle and strict, and the entire determination should be finished within 24h.

**Statistical analysis**

The sample size was subjected to hypothesis test on the difference between the mean values of the data in the two groups, and the estimated formula calculation for the required sample size was \( n = n_2 = 2(\frac{t_a + t_b}{s_d})^2 \) \( t_a = 0.05, b = 0.2 \). It was considered statistically significant if there were 26 people in each group. SPSS11.5 statistical software was used for the analysis of the experimental results. The measurement data were firstly subjected to normal distribution test and then variance analysis was carried out after it was considered similar to normal distribution; Paired t-test was used before and after the drug administration and the numeration data were subjected to quadruple tabular form² test; Moreover, simple linear correlation and regression, multiple correlation analysis and logistic regression were used.

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*Journal of Geriatric Cardiology* December 2008 Vol 5 No 4
Results

All the 125 patients were examined, among which 74 were male and 51 were female, aged 71.82±10.23 years in average. There was no significant difference in age, hypertension, diabetes, hyperlipoidemia and smoking history in patients from the three groups, and no significant difference was found in the comparison in the ejection fraction score, leukocyte counting, platelet counting and hemoglobin counting in the three groups. No significant difference was found in the number of stenosed coronary vessel, stenting operation and bypass operation of coronary artery in patients from the three groups, and no significant difference was found in the comparisons in the ejection fraction score, leukocyte counting, platelet counting and hemoglobin counting in the three groups. No significant difference was found in the number of stenosed coronary vessel, stenting operation and bypass operation of coronary artery in patients from the three groups. Thirty cases were included in the control group, among which 16 were male and 14 were female, aged 68.25±11.93 years in average. There is no significant difference in comparison of patients from the above-mentioned three groups.

Platelet aggregation rate

Platelet aggregation rate induced by 10μmol/L ADP

The platelet aggregation rates that were induced by 10μmol/L ADP in the 3 groups were all higher than that of the control group on admission. However, no significant difference can be found through the platelet aggregation rates in the 3 groups, which were still higher than that of the control group one week after the drug administration. Significant differences can be found before and after the drug administration. The platelet aggregation rate in the intravenous group showed a decrease in comparison to those of the oral administration groups, but no significant difference was found in the comparison in the decreasing rates of different groups (Table 1).

Platelet aggregation rate induced by 0.5mg/ml arachidonic acid (AA)

The platelet aggregation rates that were induced by 0.5mg/ml AA in the intravenous group, the oral administration group (100mg/d) and the oral administration group (300mg/d) were all higher than that of the control group on admission; the platelet aggregation rates in the intravenous group and the oral administration groups (100mg/d and 300mg/d) were still higher than that of the control group one week after the drug administration. Significant differences can be found in the groups before and after the drug administration. No significant difference was found between the oral administration group (100mg/d) and control group, and no significant difference was found in the decreasing rates among the 3 groups (Table 2).

Platelet CD62p level

The platelet CD62p levels of the 3 groups were all higher than that of the control group on admission; the platelet CD62p level in the oral administration group (300mg/d) was still significantly higher than that of the control group one week after the drug administration; no significant difference was found in platelet CD62p level in the intravenous group and the oral administration group (100mg/d) in comparison to that of the control group as well as the decreasing rates in platelet CD62p in the three treatment groups, and significant difference can be found in the 3 groups before and after the drug administration (Table 3).

Adverse effects

No adverse effect was found at one week in the three

Table 1 The highest aggregation rates and changing rates induced by 10μmol/L ADP in different groups on admission and after one week

<table>
<thead>
<tr>
<th></th>
<th>Intravenous administration 300 mg / d (n =40)</th>
<th>Oral administration 100 mg / d (n =42)</th>
<th>Oral administration 300 mg / d (n =43)</th>
<th>Control (n =30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission (%)</td>
<td>54.41± 15.62a</td>
<td>47.21± 17.32 *</td>
<td>4.64± 17.01a</td>
<td>37.65± 10.68</td>
</tr>
<tr>
<td>One week (%)</td>
<td>41.93± 15.13Δ</td>
<td>41.45± 11.47 Δ</td>
<td>44.92± 19.38Δ</td>
<td></td>
</tr>
<tr>
<td>Decreased rate (%)</td>
<td>12.01± 10.45</td>
<td>6.76± 14.62</td>
<td>9.73± 16.72</td>
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</tbody>
</table>

It was considered as significant difference for P<0.05 and P<0.01 in comparison to that of the control group; *P<0.01 in comparison to that of the same group on admission

Table 2 The highest aggregation rates and the changing rates that were induced by 0.5mg/ml AA in different groups on admission and after one week

<table>
<thead>
<tr>
<th></th>
<th>Intravenous administration 300 mg / d (n =40)</th>
<th>Oral administration 100 mg / d (n =42)</th>
<th>Oral administration 300 mg / d (n =43)</th>
<th>Control (n =30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>On admission (%)</td>
<td>18.67± 14.82 *</td>
<td>18.83± 14.67 *</td>
<td>24.42 ± 17.45 a</td>
<td>7.82 ± 4.46</td>
</tr>
<tr>
<td>One week (%)</td>
<td>14.64± 11.64 Δ</td>
<td>11.68± 6.87 Δ</td>
<td>16.67 ± 15.34 Δ</td>
<td></td>
</tr>
<tr>
<td>Decreased rate (%)</td>
<td>6.73± 11.34</td>
<td>6.95± 12.45</td>
<td>7.57 ± 13.11</td>
<td></td>
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</table>

It was considered as significant difference for P<0.05 and P<0.01 in comparison to that of the control group; *P<0.01 in comparison to that of the same group on admission
Aspirin blocks the synthesis of thromboxane by inhibiting cyclooxygenase and damage the enzyme active center. It can inhibit arachidonic acid metabolism in the cytosol of platelets and the platelet activation and reduce the expressions of platelet particle CD62p and GPⅡb/Ⅲa. The correlation between the dosage and the pharmacodynamic action of aspirin. In aspirin at 100-300mg/day, small dosages that were no more than 300mg had antiplatelet functions; aspirin at 500-3g/day, middle dosages had effects on relieving fever and eliminating pain; aspirin at a dosage of more than 4g/day, big dosages had anti-inflammatory and anti-rheumatism effects, and 300 mg was selected in the intravenous group in this investigation. No significant difference was found in the changing rate of ADP and AA induced platelet aggregation rates and the decreasing rate of CD62p level in the oral administration groups, indicating that these two dosages were both effective and the results were in accordance with the results of investigations from other countries in the world.

Aspirin is a weak acidic drug that stretches across the mucosal membrane of the stomach and the upper gastrointestinal tract in a lipophilic form, and the peak value of blood drug concentration can be achieved within 30-40 minutes after taking immediately dissolved aspirin and 3-4 hours after taking enteric coated tablets. Since aspirin is absorbed by the stomach and upper gastrointestinal mucosal membrane, some of them are hydrolyzed into an inactive form of salicylic acid by mucosal esterase. Inhibition of acid secretion by proton pump inhibitors can increase the potency of mucosal esterase to hydrolyze aspirin into inactive products, and thus the intestinal absorption of (active) acetyl salicylic acid is reduced, and this is one of the disadvantages of oral metabolic pathway. Among patients that suffer from acute coronary syndrome and comatose or fasting patients that can not take drugs orally are common, and some simultaneously take other oral drugs such as proton pump inhibitors, non-steroidal anti-inflammatory drugs and others, which may affect the absorption and pharmacodynamic action of orally administered aspirin by drug interactions. Orally administered aspirin had direct stimulations to the mucosal membrane of digestive tract in patients with digestive diseases. Unconscious patients can be handled by introducing grinded aspirin orally into the canal of stomach during the anti-platelet treatment in acute stage, but no effective method had been found for fasting patients, patients suffering from reactive peptic ulcer or bleeding and those taking proton pump inhibitors and non-steroidal anti-inflammatory drugs simultaneously. Furthermore, intravenous preparation is 1.8 times of the blood drug concentration that is administered orally, and its concentration increases rapidly after the intravenous injection, which can avoid the direct stimulus to the mucosal membrane of the digestive tract and the interactions with proton pump inhibitors and non-steroidal anti-inflammatory drugs that are taken orally.

The study that was carried out by Wan et al in our country found that the platelets in the ASC patients were in group that no complaints from the patients and no bleeding in the six weeks of follow-up. In the oral administration group (100mg/d), we found one case of coughing up blood, one case of massive hemorrhage of gastrointestinal tract (incidence rate of bleeding 4.8%). In the oral administration group (300mg/d), we found one case of dark stools, and the incidence rate of bleeding (2.3%) is similar to that of the intravenous group after 2 tests (P>0.05). The cases that underwent adverse effects of bleeding were all senile patients over 75 years old.

The logistic regression analysis for the clinical incidents in the three groups and the correlation factors

The three groups were all subjected to secondary preventive medication for coronary heart disease after discharge, and the situations of drug administration were similar. The results of the follow-up in the six months were as followed: four cases (10%) of clinical incidents were found in the intravenous group, four (9.5%) and five cases (11.6%) in the oral administration group (100mg/d and 300mg/d, respectively). Relative impact factors were subjected to logistic regression analysis, including platelet aggregation rate (ADP and AA), platelet CD62p level, hs-crp, Fib, ejection fraction of the left ventricle (EF), PLT, Hb, the number of stenosed coronary vessel, whether the blood vessels were reconstructed, age, gender, cardiac function grade IV and smoking. The logistic regression analysis revealed that the relative factors were LVEF (P=0.001) and blood hs-crp (P=0.026).

Table 3 CD62p levels and the changing rates in different groups on admission and after one week

<table>
<thead>
<tr>
<th></th>
<th>Intravenous administration</th>
<th>Oral administration</th>
<th>Oral administration</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg / d (n =40)</td>
<td>100 mg / d (n =42)</td>
<td>300 mg / d (n =43)</td>
<td>(n=30)</td>
</tr>
<tr>
<td>On admission (%)</td>
<td>27.89±19.54*</td>
<td>28.34±15.45*</td>
<td>32.87±17.58*</td>
<td>16.78±8.56</td>
</tr>
<tr>
<td>One week (%)</td>
<td>16.93±11.43 △</td>
<td>19.35±10.46 △</td>
<td>25.67±16.54*</td>
<td></td>
</tr>
<tr>
<td>Decreased rate (%)</td>
<td>10.89±18.62</td>
<td>8.92±11.57</td>
<td>7.05±15.67</td>
<td></td>
</tr>
</tbody>
</table>

It was considered as significant difference for P<0.05 and *P<0.01 in comparison to that of the control group; #P<0.01 in comparison to that of the same group on admission.
a highly activated status, and the determination of CD62p level can be used as an effective index for the monitoring of coronary heart disease. In this experiment, no significant difference was found in the decreasing rates of ADP-induced platelet aggregation rates or in the decreasing rates of AA-induced platelet aggregation rates in 3 groups; and no significant difference was found in the comparison in the decreasing degree of CD62p levels in 3 groups. The results indicated that intravenous administration can be utilized in the acute stage or during the hospitalization for patients with digestive diseases and fasting acute coronary syndrome, and patients taking other orally administered drugs (these drugs can affect the absorption and pharmacodynamic action for interactions) such as proton pump inhibitors and non-steroidal anti-inflammatory drugs.

Common adverse effects include hemorrhagic complications, gastrointestinal irritation and diarrhea, and rash. No hemorrhagic complications and adverse effects were found within one week after the drug administration in the intravenous administration group in this investigation, and intravenous aspirin injection did not show stimulation to the blood vessels (no complaints from the patients), and no adverse effect was found in the intravenous administration group. Furthermore, no significant difference was found in the clinical events that occurred within six months of the follow-up in the three groups (including recurred acute myocardial infarction, rehospitalization and coronary revascularization, cardiac death during the hospitalization and the follow-up, death due to other reasons and acute cerebral infarction), indicating that intravenous administration of aspirin is a feasible and effective route.

References