Effect of Dialysis on Antiplatelet Drug Efficacy in Uremic Patients with Coronary Heart Disease

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Abstract

Background: Coronary intervention therapy is the main treatment for uremic patients with coronary heart disease. The studies on whether dialysis reduces the efficacy of dual antiplatelet drugs are limited. The aim of this study was to examine the effect of dialysis on antiplatelet drugs in uremic patients with coronary heart disease.

Methods: This study included 26 uremic patients who had undergone percutaneous coronary intervention in China-Japan Friendship Hospital from November 2015 to May 2017. We examined their thromboelastography results before and after hemodialysis. Self-paired t-tests were employed to analyze changes in the inhibition rate of platelet aggregation.

Results: The mean inhibition rates of arachidonic acid-induced platelet aggregation before and after hemodialysis were 82.56 ± 2.79% and 86.42 ± 3.32%, respectively (t = -1.278, P = 0.213). The mean inhibition rates of adenosine diphosphate-induced platelet aggregation before and after hemodialysis were 67.87 ± 5.10% and 61.94 ± 5.90%, respectively (t = 1.425, P = 0.167). There was no significant difference in the inhibition rates of platelet aggregation before or after hemodialysis. These results also applied to patients with different sensitivity to aspirin and clopidogrel.

Conclusion: Dialysis did not affect the antiplatelet effects of aspirin and clopidogrel in uremic patients with coronary heart disease.

Key words: Antiplatelet Drug; Coronary Intervention; Dialysis; Thromboelastography

Introduction

The incidence of coronary heart disease in uremic patients is three times higher than that in the general population.1 Even in patients undergoing hemodialysis treatment, cardiovascular complications are still the leading cause of death. The primary treatment for uremic patients with coronary heart disease is drug therapy, which is not effective, however, in patients with severe coronary heart disease. For these patients, either coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI) can be performed to achieve revascularization.2 Due to their poor health status, uremic patients are predisposed to many complications such as heart failure, hemorrhage, and infection during the perioperative period, with a relatively high operative mortality rate.3 In China, surgeons rarely perform CABG on uremic patients. As coronary intervention therapies (especially rotational atherectomy) are developed, uremic patients are more willing to undergo coronary intervention therapies to treat coronary heart disease.

Stent thrombosis is an unavoidable problem following coronary intervention. Factors that facilitate the prevention of stent thrombosis include suitable operation procedures, appropriate stent material and technique, and antiplatelet agents, which particularly play a major role in preventing stent thrombosis.4 However, uremic patients require long-term hemodialysis treatment, which may eliminate aspirin and clopidogrel from systemic circulation.

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Evidence-based medicine offers little information on whether hemodialysis can decrease the efficacy of dual antiplatelet agents, or whether long-term hemodialysis may increase the risk of stent thrombosis.

In clinical practice, the use of thromboelastography (TEG) as a detection tool plays an important role in evaluating platelet activity and can indicate the efficacy of antiplatelet treatment in patients with coronary heart disease or aspirin or clopidogrel resistance.[19] This study performed TEG to examine changes in platelet aggregation inhibition rates before and after hemodialysis, to investigate whether hemodialysis affects the efficacy of dual antiplatelet agents (aspirin and clopidogrel) in uremic patients with coronary heart disease. The results could provide evidence-based support for the current interventional therapy provided to these patients.

**Methods**

**Ethical approval**

Informed consent was obtained from all the research participants. The study was approved by China-Japan Friendship Hospital’s Institutional Ethical Review Board, and all patients were provided with written informed consent for participation. The study conformed to the principles outlined in the Declaration of Helsinki.

**Patients**

Twenty-six uremic patients (17 males and 9 females) were included in the study. These patients were admitted to the Department of Cardiology, China-Japan Friendship Hospital and received PCI from November 2015 to May 2017. Patients had been diagnosed with coronary heart disease (including stable angina, unstable angina, or acute myocardial infarction) according to standard diagnostic and treatment guidelines.[6,7] Patients were also diagnosed with Stage 5 chronic kidney disease and were receiving regular treatment, which included hemodialysis (three times/week) or continuous renal replacement therapy (three to four times/week, more than 4 h each time). Patients also received the loading dose of dual antiplatelet drugs before coronary intervention and received regular aspirin and clopidogrel dual antiplatelet therapy postoperatively.

The exclusion criteria were as follows: (1) platelet count >450 × 10⁹/L or <100 × 10⁹/L; (2) patients who had received oral anticoagulants or other antiplatelet drugs 2 weeks before surgery; (3) abnormal coagulation or severe liver disease; or (4) severe anemia, infection, or hyperthyroidism.

**Platelet function assessment**

Blood samples were collected 3 days after PCI by peripheral venipuncture. Within 6 h before dialysis, 4 ml of peripheral venous blood was collected from the patients; another 4 ml of peripheral venous blood was collected within 6 h after dialysis. Blood samples were placed in a sodium citrate anticoagulated vacuum blood collection tube and mixed thoroughly. The platelet aggregation inhibition rate test (i.e., 80-item TEG: arachidonic acid [AA] for aspirin and adenosine diphosphate [ADP] for clopidogrel) was performed within 2 h after blood sample collection. This test was performed using the TEG® 5000 Thrombelastograph® Hemostasis Analyzer (Haemonetics, Braintree, MA, USA).

**Indicators**

We used platelet aggregation inhibition rates before and after hemodialysis as indicators; these included the inhibition rate of AA- and ADP-induced platelet aggregation, which were targeted by aspirin and clopidogrel, respectively. An inhibition rate of AA-induced platelet aggregation ≥50% was considered sensitive to aspirin; <50% was considered insensitive to aspirin. An inhibition rate of ADP-induced platelet aggregation ≥50% was considered sensitive to clopidogrel; <50% was considered weakly reactive and unresponsive, i.e., insensitive.

**Statistical analysis**

Demographic characteristics and results of platelet inhibition test were described firstly. Continuous variables are presented as mean ± standard deviation (SD) or range, and categorical variables are shown as number and percentages. The paired t-test was applied to access the differences of inhibition rate for AA- and ADP-induced platelet aggregation pre- and post-hemodialysis. In addition, a subgroup analysis was conducted on patients with the inhibition rate for ADP-induced platelet aggregation <50% and that of ≥50% at pre-hemodialysis. Statistical analyses were performed using SAS 9.13 (SAS Institute Inc., Cary, NC, USA). All tests were two tailed and P < 0.05 was considered statistically significant.

**Results**

**Characteristics of patients**

In this study, 26 patients were investigated, with an average age of 63.2 years, and a duration of dialysis of 12–240 months (39.6 ± 5.2 months), a single dialysis session lasted 4–6 h, and was carried out three times/week. All patients had undergone coronary intervention for coronary artery disease and continued to be treated with aspirin and clopidogrel for 1 year. The clinical and laboratory characteristics of the patients are listed in Table 1.

**Platelet aggregation inhibition before and after hemodialysis**

Data from the platelet aggregation inhibition test before and after hemodialysis are shown in Table 2. For aspirin, the inhibition rate of AA-induced platelet aggregation was ≥50% in 25 patients before dialysis, and the inhibition rate was <50% in just one patient, thus 3.8% of patients were not sensitive to aspirin. For clopidogrel, the inhibition rate of ADP-induced platelet aggregation was ≥50% in 19 patients before dialysis, and the inhibition rate was <50% in 7 patients, thus 27% of patients had a low or ineffective response to clopidogrel.

**Comparison of the inhibition rates of arachidonic acid-induced platelet aggregation**

TEG results for the 26 patients showed that the mean inhibition rates for AA-induced platelet aggregation pre- and
Relationship between dialysis and aspirin sensitivity

In this study, the inhibition rate of AA-induced platelet aggregation was <50% for just one patient before dialysis, and the inhibition rate remained <50% after dialysis. For the other 25 patients, inhibition rates were ≥50% before dialysis, and inhibition rates remained ≥50% after dialysis. Therefore, dialysis did not affect the antiplatelet effect of aspirin, which also applied to patients with different sensitivity to aspirin.

Comparison of the inhibition rates of adenosine diphosphate-induced platelet aggregation

The mean inhibition rates for ADP-induced platelet aggregation pre- and post-hemodialysis were 67.87 ± 5.10% and 61.94 ± 5.90%, respectively, which were not statistically significantly different (t = 1.278, P = 0.213) [Table 3].

Relationship between dialysis and clopidogrel sensitivity

In this study, the inhibition rate of ADP-induced platelet aggregation was ≥50% before dialysis, and the inhibition rate remained ≥50% after dialysis. Therefore, dialysis did not affect the antiplatelet effect of aspirin, which also applied to patients with different sensitivity to aspirin.

Discussion

Maintenance hemodialysis is the main treatment for patients with uremia. Among uremic patients who undergo hemodialysis, both the incidence and mortality rates of coronary heart disease are significantly higher (over three times) than those of the general population.[9] Acute coronary syndrome is the most common coronary heart disease in uremic patients, which is usually an urgent medical condition; pathologic changes in the coronary artery are relatively serious, and the efficacy of drug treatment is poor.[9] As coronary intervention can rapidly alleviate symptoms and reduce adverse cardiac events in these patients, an increasing number of uremic patients with coronary heart disease tend to undergo coronary interventions.

Postoperative dual antiplatelet therapy is indicated for 1 year to prevent coronary stent thrombosis after coronary intervention. Furthermore, uremic patients are dependent on long-term dialysis. Our results show that the inhibition rates of AA- and ADP-induced platelet aggregation did not change significantly before and after hemodialysis. We can therefore conclude that hemodialysis does not significantly influence the effects of dual antiplatelet therapy with aspirin or clopidogrel.

The mechanisms of action of aspirin and clopidogrel can explain why hemodialysis does not affect the efficacies of these dual platelet inhibitors. Both aspirin and clopidogrel prevent thrombus formation by inhibiting platelet aggregation, but they exert their function through different pathways.[10] Aspirin inhibits platelet aggregation through a pathway induced by thromboxane A2 (TXA2), while clopidogrel acts on a different pathway induced by ADP. Aspirin causes cyclooxygenase (COX) to permanently lose its activity, which inhibits TXA2 generation in platelets. TXA2 has a strong stimulating effect on platelet aggregation, while aspirin inhibits platelet aggregation through a pathway induced by TXA2 generation.[12] Although dialysis may remove some of the aspirin, platelets have been permanently inhibited once post-hemodialysis were 82.56 ± 2.79% and 86.42 ± 3.32%, respectively, which were not statistically significantly different (t = 1.327, P = 0.201).

Values statistically significant difference (t = 1.327, P = 0.201). Therefore, dialysis did not affect the antiplatelet effect of clopidogrel, which also applied to patients with different sensitivity to clopidogrel.

Table 1: Clinical and laboratory characteristics of uremic patients who had undergone percutaneous coronary intervention (n = 26)

| Characteristic                              | Values                  |
|--------------------------------------------|-------------------------|
| Age (years)                                | 63.2 ± 9.3              |
| Male, n (%)                                | 17 (65)                 |
| BMI (kg/m²)                                | 23.67 ± 3.52            |
| Duration of dialysis (months)              | 39.6 ± 5.2              |
| Risk factor, n (%)                         |                         |
| Current smoking                            | 6 (23)                  |
| Diabetes mellitus                          | 16 (62)                 |
| Hypertension                               | 19 (73)                 |
| Hyperlipemia                               | 15 (58)                 |
| Type of CHD, n (%)                         |                         |
| SAP                                        | 3 (12)                  |
| UAP                                        | 8 (31)                  |
| AMI                                        | 15 (58)                 |
| Laboratory measurements                    |                         |
| Platelet (×10¹²/L)                         | 216.00 ± 45.36          |
| Hemoglobin (g/L)                           | 115.36 ± 16.23          |
| ALT (U/L)                                  | 44 (22–76)              |
| Serum creatinine (µmol/L)                  | 577.5 (469.2–989.8)     |
| Glucose (mmol/L)                           | 8.16 (5.67–9.77)        |
| LDL-C (mmol/L)                             | 3.14 ± 0.98             |
| LVEF (%)                                   | 47.60 (36.00–68.00)     |
| Concomitant medications, n (%)             |                         |
| ACEI or ARB                                | 14 (54)                 |
| Beta-blocker                               | 22 (85)                 |
| Nitrates                                   | 12 (46)                 |
| Statin                                     | 24 (92)                 |
| PPI                                        | 21 (81)                 |

The data were presented as n (%), median (IQR), or mean ± SD. SD: Standard deviation; IQR: Interquartile range; BMI: Body mass index; SAP: Stable angina pectoris; UAP: Unstable angina pectoris; AMI: Acute myocardial infarction; ALT: Alanine transaminase; LDL-C: Low-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; PPI: Proton pump inhibitor.

Postoperative dual antiplatelet therapy is indicated for 1 year to prevent coronary stent thrombosis after coronary intervention. Furthermore, uremic patients are dependent on long-term dialysis. Our results show that the inhibition rates of AA- and ADP-induced platelet aggregation did not change significantly before and after hemodialysis. We can therefore conclude that hemodialysis does not significantly influence the effects of dual antiplatelet therapy with aspirin or clopidogrel.
the aspirin level reaches a loading dose. Therefore, partially removing the drug does not alter platelet aggregation inhibition over a short period of time. There is a similar mechanism for clopidogrel, which functions as an ADP receptor antagonist that can selectively inhibit the binding of ADP to the platelet receptor. Activation of the ADP and glycoprotein GPIIb/IIIa complex is thus prevented, resulting in irreversible inhibition of platelet aggregation. Partially removing clopidogrel does not change this scenario. Collectively, our results indicate that dialysis does not have an obvious impact on the effect of dual antiplatelet therapy with aspirin and clopidogrel. In patients with different drug sensitivity, the effect of dialysis on aspirin and clopidogrel is consistent.

Standard treatment for uremic patients with coronary heart disease is still being developed. It is difficult for physicians to treat these patients due to the lack of evidence-based treatments. The present study indicates that dialysis does not affect the efficacy of dual antiplatelet treatment. There is no significant increase in the incidence rate of stent thrombosis in uremic patients undergoing coronary intervention. If there is no contraindication, coronary artery intervention can be proactively used in uremic patients to relieve their symptoms and improve prognosis.

This study is limited in several respects. First, as the uremic patient population is relatively small, there are a limited number of patients undergoing interventional therapy in a single center. The lack of statistical significance may have been due to the relatively small sample size. Second, this was a single-center study with a simple test method, so the results may have been affected by factors such as detection techniques and testing methods employed at our hospital.

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| List | Prehemodialysis | Posthemodialysis | Prehemodialysis | Posthemodialysis |
|------|-----------------|------------------|-----------------|------------------|
| 1    | 84.40           | 88.20            | 92.30           | 86.70            |
| 2    | 94.00           | 99.10            | 98.10           | 94.80            |
| 3    | 69.70           | 96.80            | 41.00           | 24.70            |
| 4    | 91.50           | 82.90            | 96.10           | 98.80            |
| 5    | 83.40           | 79.30            | 33.70           | 7.90             |
| 6    | 80.00           | 94.40            | 33.90           | 33.80            |
| 7    | 36.40           | 14.40            | 92.80           | 98.90            |
| 8    | 98.40           | 84.50            | 49.30           | 36.90            |
| 9    | 74.80           | 80.20            | 15.40           | 19.80            |
| 10   | 97.70           | 94.80            | 99.10           | 77.80            |
| 11   | 78.47           | 98.10            | 58.80           | 14.50            |
| 12   | 53.60           | 81.80            | 74.50           | 94.90            |
| 13   | 68.90           | 95.70            | 15.80           | 51.10            |
| 14   | 84.50           | 92.00            | 78.50           | 84.60            |
| 15   | 89.30           | 93.60            | 79.80           | 81.10            |
| 16   | 82.30           | 98.60            | 66.80           | 94.80            |
| 17   | 89.80           | 87.60            | 86.30           | 74.60            |
| 18   | 75.40           | 92.30            | 53.60           | 30.00            |
| 19   | 96.40           | 79.20            | 98.60           | 33.90            |
| 20   | 96.90           | 89.70            | 95.40           | 80.00            |
| 21   | 91.20           | 80.10            | 60.60           | 78.30            |
| 22   | 76.60           | 98.30            | 70.90           | 55.70            |
| 23   | 86.90           | 65.20            | 80.10           | 92.30            |
| 24   | 88.40           | 96.90            | 44.50           | 33.40            |
| 25   | 79.30           | 97.80            | 93.10           | 84.00            |
| 26   | 98.30           | 85.40            | 55.60           | 47.10            |

AA: Arachidonic acid; ADP: Adenosine diphosphate.

| Inhibition rates of platelet aggregation | n (male/female) | Predialysis (%) | Postdialysis (%) | t   | P   |
|----------------------------------------|-----------------|-----------------|-----------------|-----|-----|
| AA-induced                             | 26 (17/9)       | 82.56 ± 2.79    | 86.42 ± 3.32    | −1.278 | 0.213 |
| ADP-induced                            | 26 (17/9)       | 67.87 ± 5.10    | 61.94 ± 5.90    | 1.425 | 0.167 |

AA: Arachidonic acid; ADP: Adenosine diphosphate.
Conflicts of interest

There are no conflicts of interest.

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