Effect of a small dose of aspirin on quantitative test of 24-h urinary protein in patients with hypertension in pregnancy

FANGMEI LIU¹, HUILI YANG¹, GUIYUN LI², KUN ZOU¹ and YANA CHEN¹

¹Department of Obstetrics and Gynecology, Jinan Central Hospital, Shandong University, Jinan, Shandong 250013; ²Department of Obstetrics and Gynecology, The First People's Hospital of Jinan, Jinan, Shandong 250000, P.R. China

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Abstract. The aim of the present study was to determine the effect of a small dose of aspirin on a quantitative test of 24-h urinary protein in patients with hypertension in pregnancy. In total, 224 patients with hypertension in pregnancy were continuously selected and were randomly divided into the control group (50 cases with conventional therapy), aspirin 50 mg/day group (60 cases), aspirin 75 mg/day group (58 cases), and aspirin 100 mg/day group (56 cases). Clinical effects were compared from 16 gestational weeks to childbirth. According to the comparison in the four groups, there was no statistical difference in the mean arterial pressure, pre-eclampsia rate, gestational weeks, and caesarean section rate (p>0.05). The 24-h urinary protein and endothelin-1 (ET-1) level were significantly decreased following treatment, and were less than the control and 50 mg/day groups. The superoxide dismutase (SOD) level was significantly increased, and higher than the control and 50 mg/day groups. In terms of the 75 and 100 mg/day, control and 50 mg/day groups, there was no statistical difference (p>0.05). A comparison of the complication rate in the four groups of fetuses during the perinatal period, no statistical difference was observed (p>0.05). Thus, the results show that, regarding patients with hypertension in pregnancy, 75 mg/day aspirin can decrease the 24-h urinary protein, SOD, and ET-1 level. However, the results remain to be confirmed to improve maternal and infant outcome in delivery.

Introduction

Hypertension in pregnancy is a common disease that exhibits clinical characteristics including hypertension, edema, albuminuria, twitch, coma, heart and renal failure, and even maternal-fetal death (?). The 2013 guidelines for hypertension in pregnancy released by ACOG recommends that it is essential to have a quantitative test of 24-h urinary protein and diagnosis of pre-eclampsia (1). Additionally, with biochemical indices such as superoxide dismutase (SOD) and endothelin-1 (ET-1), the accuracy of diagnosis may be highly improved in the early stage of pre-eclampsia.

For patients at high risk of suffering from pre-eclampsia a small dose of aspirin (60-80 mg/day) is considered safe and effective. Although recording of the starting time and administration of aspirin to patients with hypertension in pregnancy is a recent phenomenon in China, previous findings have shown that aspirin (50 mg/day) is definitely beneficial to reduce the incidence of pre-eclampsia and intracranial hemorrhage of fetus (2). In addition, aspirin at a dose of 100 mg/day may be more beneficial than 50 mg/day without increasing complications during the perinatal period (3).

The present randomized, double-blind and clinical control study was performed to determine whether a small dose of aspirin is useful to patients with hypertension in pregnancy.

Patients and methods

A total of 224 patients with hypertension in pregnancy were successively selected from October, 2012 to October, 2015, at the Jinan Central Hospital (Shandong, China). The inclusion criteria for the study were: i) ≥18 but <50 years of age; ii) in accordance with 2013 standards for hypertension in pregnancy issued by ACOG, but with high risk of pre-eclampsia such as >40 years, obesity, chronic hypertension, chronic kidney disease, type 1 or 2 diabetes mellitus, family history of pre-eclampsia, previous pregnancy along with pre-eclampsia, thrombosis history, and systemic lupus erythematosus; iii) single birth; and iv) no past history of having aspirin and anticoagulant medications such as warfarin, and no complications such as rheumatic disease and chronic atrial fibrillation that require ingesting aspirin or warfarin. The exclusion criteria were: i) artificial insemination; ii) coagulation disorders; iii) hard to control medication for hypertension in pregnancy; iv) an allergy to aspirin; and v) bad compliance.

The present study was approved by the ethics committee of the Jinan Central Hospital. Written informed consent was obtained from the patients. According to the order of hospitalization, patients were randomly divided into the control group

Correspondence to: Dr Yana Chen, Department of Obstetrics and Gynecology, Jinan Central Hospital, Shandong University, 44 Wenhua Xi Road, Jinan, Shandong 250013, P.R. China
E-mail: mifdpmx51081@163.com

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and the manufacturer’s instructions were strictly followed. Use of aspirin, whereas radioimmunoassay was used for ET-1. Kits were removed by centrifugation at 2,800 x g after 30 min, and kept at 4˚C for the test. For SOD the xanthine oxidase method was collected on an empty stomach. The upper stratum was used, whereas radioimmunoassay was used for ET-1. Kits were purchased from R&D Systems, Inc. (Minneapolis, MN, USA), and the manufacturer’s instructions were strictly followed.

Observation index. Patients were divided into four groups to determine differences in MAP, pre-eclampsia incidence, gestational weeks and the caesarean section rate, test of 24-h urinary protein, SOD and ET-1, and complications during the perinatal period. For SOD and ET-1 peripheral blood of 5 ml was collected on an empty stomach. The upper stratum was used, whereas radioimmunoassay was used for ET-1. Kits were purchased from R&D Systems, Inc. (Minneapolis, MN, USA), and the manufacturer’s instructions were strictly followed.
and E through lots of random tests and case-control study on placebo has been shown not to be useful (9). Urinary protein is a sign of early hypertensive kidney lesion and of disease progression as in the case of pre-eclampsia (10). Different levels of urinary protein are positively correlated with the degree of blood pressure (11). An increase of urinary protein may lead to the ultrastructure of the local spherule-tubule cell in kidney to change, and the electrical load to be raised. Furthermore, urinary protein may leak out under such poor circulation. Additionally, there is disorder in the local part of the kidney, whole oxygen-free radical metabolism, and vascular endothelial cell (12). Active metabolism in placenta, higher oxygen consumption, more oxygen-free radicals, and a balance of oxidation and anti-oxidation are major factors in the prevention of pre-eclampsia (13). SOD is a free radical scavenger that lies in the cells of aerobic metabolism. It plays a role in controlling the balance of creating and removing free radicals (14). Previous findings have shown that a certain dose of aspirin (75 and 100 mg) may raise the SOD level, relieve oxidation reactions and improve metabolism in urinary protein (15).

Owing to feeding cells, the placenta is likely to undergo hypoxia and ischemia and then release a variety of inflammatory factors including ET-1 with vasoconstriction. In addition, with the damage in vascular endothelial cells, internal and external coagulation mechanism may function. Thus, platelet aggregation is associated with thrombus formation (16). ET-1 lies in endothelial cells, which is the most vasoactive substance. It increases obviously during the middle and late pregnancy of normal pregnant women, but also increases in women with hypertension. There is a close relationship with pre-eclampsia in incidence and severity (17). Aspirin is important in retarding platelet aggregation and thrombus formation by inhibiting the activity of epoxidase, interfering arachidonic

### Table I. Comparison of MAP, pre-eclampsia rate, gestational weeks and caesarean section.

| Groups       | Cases | Before MAP (mmHg) | After MAP | Pre-eclampsia | Gestational week (weeks) | Caesarean section |
|--------------|-------|------------------|----------|---------------|------------------------|------------------|
| Control      | 50    | 115.8±15.9       | 88.2±13.2| 16 (32.0)     | 35.6±3.3               | 6 (12.0)         |
| 50 mg/day    | 60    | 117.6±16.7       | 86.4±14.6| 22 (36.7)     | 36.4±3.5               | 7 (11.7)         |
| 75 mg/day    | 58    | 114.4±18.2       | 85.8±12.7| 20 (34.5)     | 36.2±3.6               | 8 (13.8)         |
| 100 mg/day   | 56    | 109.2±20.2       | 86.6±16.9| 21 (37.5)     | 35.8±3.7               | 7 (12.5)         |
| F            |       | 0.526            | 0.637    | 0.423         | 0.836                  | 0.138            |
| P-value      |       | 0.325            | 0.421    | 0.935         | 0.725                  | 0.987            |

### Table II. Comparison of 24-h urinary protein, SOD and ET-1.

| Groups       | Before urinary protein (g) | SOD (nU/ml) | ET-1 (ng/l) |
|--------------|---------------------------|-------------|-------------|
| Control      | 2.3±0.9 1.8±0.5 1.201 0.967 | 46.7±13.5 53.4±15.2 0.637 | 86.5±20.1 83.4±26.9 0.467 |
| 50 mg/day    | 2.4±0.8 1.6±0.7 1.367 0.768 | 48.2±14.9 55.9±16.9 0.938 | 85.2±23.5 81.6±23.5 0.539 |
| 75 mg/day    | 2.5±0.7 0.9±0.4 4.938 0.039 | 46.9±16.3 127.4±34.5 5.634 | 88.4±24.6 48.5±14.7 6.324 |
| 100 mg/day   | 2.3±0.8 1.1±0.6 5.022 0.037 | 47.5±18.5 113.8±33.6 5.705 | 87.5±28.7 46.3±16.9 6.532 |
| F            | 0.635 5.624 0.837 5.768 | 0.323 | 6.967 |
| P-value      | 0.427 0.033 0.639 0.031 | 0.218 | 0.975 |

SOD, superoxide dismutase; ET-1, endothelin-1.

### Table III. Comparison of complications during the perinatal period (cases %).

| Groups       | Cases | Intracranial and ventricular hemorrhage | Ischemia, hypoxia | Placental abruption | Death | Complication rate |
|--------------|-------|----------------------------------------|-------------------|---------------------|-------|-------------------|
| Control      | 50    | 0                                      | 2                 | 1                   | 1     | 4 (8.0)           |
| 50 mg/day    | 60    | 1                                      | 3                 | 0                   | 1     | 5 (8.3)           |
| 75 mg/day    | 58    | 2                                      | 3                 | 0                   | 1     | 6 (10.3)          |
| 100 mg/day   | 56    | 2                                      | 1                 | 1                   | 1     | 5 (8.9)           |
| χ²           |       |                                        | 0.218             |                     |       | 0.975             |
| P-value      |       |                                        | 0.975             |                     |       |                   |
acid to TXA2 and increasing PG12 (18). Thus, a certain dose of aspirin (75 and 100 mg) plays an important role in reducing ET-1 and improving metabolism in urinary protein.

The present findings suggest that there was no statistical significance with regard to MAP, pre-eclampsia, gestational weeks and the caesarean section rate in the four groups studied. Although a certain dose of aspirin can reduce urinary protein, SOD and ET-1, whether it can change the clinical outcome is not clear. Different from the previous studies, which identified a small dose of aspirin as being capable of preventing middle and high risk pre-eclampsia, different races and samples were also taken into account in the current study. No statistical significance in the incidence of complications during the perinatal period was observed. Thus, no association between the two factors may exist.

In conclusion, 75 mg of aspirin daily can reduce 24-h urinary protein, SOD, and ET-1 in those patients with hypertension in pregnancy. Nevertheless, more studies are required to determine whether it can improve delivery outcome of mother and infant.

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