Am J Transl Res 2021;13(8):9113-9121
www.ajtr.org /ISSN:1943-8141/AJTR0134821

Original Article

The clinical effect of aspirin combined with low-molecular-weight heparin in the treatment of severe preeclampsia and the combination's effect on pregnancy outcomes

Lihua Chang[1], Yanfeng Liu[2], Xingxing Zhang[3], Ziyun Shi[4], Duomei Ren[4], Xiujuan Li[1], Yanchuan Li[4]

[1]Obstetrics, The Second Affiliated Hospital of Xi'an Medical University, Xi'an 710038, Shaanxi Province, China; [2]General Surgery, The Second Affiliated Hospital of Xi'an Medical University, Xi'an 710038, Shaanxi Province, China; [3]Clinical Laboratory, The Second Affiliated Hospital of Xi'an Medical University, Xi'an 710038, Shaanxi Province, China; [4]Obstetrics, Shanxi Provincial People's Hospital, Xi'an 710068, Shaanxi Province, China

Received April 30, 2021; Accepted June 18, 2021; Epub August 15, 2021; Published August 30, 2021

Abstract: Objective: To explore the clinical effects of aspirin combined with low-molecular-weight heparin (LMWH) in the treatment of patients with severe preeclampsia and the combination's influence on pregnancy outcomes. Methods: From October 2018 to June 2020, 104 patients with severe preeclampsia who underwent treatment in our hospital were recruited as the study cohort and divided into two groups according to different treatment scheme each patient underwent. In the research group (RG), the 54 patients were administered aspirin combined with LMWH, and the other 50 patients in the control group (CG) were administered routine treatment. The total effective rates were compared between the two groups. The blood pressure, coagulation function, hemorheology, and renal function indexes were compared before and after the therapy. The Apgar scores of the newborns and the incidences of adverse pregnancy outcomes were measured at 1 and 5 minutes after the births. Results: After the therapy, the systolic blood pressure (SBP) and the diastolic blood pressure (DBP) in the RG were lower than they were in the CG. The PT and APTT in the RG were significantly higher than they were in the CG, and the FIB and D-D were significantly lower than they were in the CG. After the treatment, the hematocrit, the erythrocyte sedimentation rate, and the plasma viscosity in the RG were significantly lower than they were in the CG. The 24 h UP, BUN, UA, and Scr levels in the RG were significantly lower than they were in the CG. The Apgar scores of the newborns in the RG were significantly higher than they were in the CG at 1 min and 5 min after the births. After the therapy, the incidence of adverse pregnancy outcomes in the RG was significantly lower than it was in the CG, and the total effective rate in the RG was significantly higher than it was in the CG. Conclusion: Aspirin combined with LMWH can effectively improve the clinical efficacy, the coagulation function, the renal function, and the blood pressure levels, and the combination can reduce adverse pregnancy outcomes in severe preeclampsia patients.

Keywords: Aspirin, low-molecular-weight heparin, severe preeclampsia, clinical effects, pregnancy outcomes

Introduction

Pre-eclampsia is defined as a systematic syndrome, and it is characterized by elevated blood pressure and proteinuria in women with normal blood pressure for 20 weeks after pregnancy [1]. The patients experience convulsions, foaming at the mouth, coma, and other symptoms. In severe cases, they will have repeated convulsions [2]. Eclampsia is one of the four major causes of death in pregnant women. If it is not treated in time, it will lead to intrauterine fetal death and can even threaten the lives and safety of pregnant women and their fetuses [3]. Other studies have revealed that patients with preeclampsia will have disseminated intravascular coagulation, which leads to an increased risk of adverse pregnancy outcomes [4]. Therefore, it is particularly important to find effective intervention methods for improving the pregnancy outcomes of patients with severe preeclampsia.

Aspirin is a non-steroidal anti-inflammatory drug [5], and it is clinically used to treat pain, fever, inflammation, etc. It is also an antiplate-

let drug and can prevent various heart diseases and stroke caused by blood coagulation [6]. Aspirin has antithrombotic effects *in vivo* and can inhibit the aggregation and release of platelets, thus improving the hypercoagulability of blood, so it is widely used in the clinical prevention of thrombosis [7]. Studies have revealed that low-dose aspirin is the most commonly-used drug to prevent preeclampsia in high-risk pregnant women [8]. However, the intervention effect of aspirin alone is not ideal, so this study was designed to combine it with LMWH (low-molecular-weight heparin) treatment. Heparin is an anti-inflammatory, anticoagulant and anti-immune drug [9], and LMWH is a commonly used anticoagulant drug in the clinic. Because of its long drug half-life, it is easily absorbed by the body [10], thus reducing the aggregation of platelets and improving or reducing thrombosis [11]. Studies have shown that LMWH can improve pregnancy outcomes by regulating many physiological processes required for blastocyst attachment, implantation, and trophoblast invasion. The subcutaneous injection of LMWH has a controllable anticoagulation effect and fewer side effects than other anticoagulants [12]. Studies by Rodger have revealed that placenta-mediated pregnancy complications include preeclampsia, placental abruption, and so on. LMWH intervention can effectively reduce the risk of the recurrence of placenta-mediated pregnancy complications [13].

This study aimed to provide information on the treatment of severe preeclampsia patients by observing the effects of aspirin combined with LMWH on the patients' clinical effectiveness and pregnancy outcomes.

Materials and methods

Baseline data

From October 2018 to June 2020, 104 patients with severe preeclampsia who underwent treatment at the Second Affiliated Hospital of Xi'an Medical University were recruited as the study cohort and divided into two groups according to different treatment scheme each patient underwent. In the RG, the 54 patients were administered aspirin combined with LMWH, and the 50 patients in the CG were administered routine treatment. This research was approved by our hospital's ethics committee (NPL-54-159), and both the patients and their guardians were informed of the study and signed the informed consent forms.

Inclusion criteria: All the patients were diagnosed with severe preeclampsia [14], and all the patients were singleton pregnancies, the patients did not take blood pressure control drugs in the previous three months, the baseline clinical data were complete, the patients were able to follow the doctor's orders to complete the relevant examinations and treatment, and the patients had no other pregnancy complications.

Exclusion criteria: Patients who quit the experiment halfway, patients with a history of allergies to the drugs used in this study, patients comorbid with hemorrhagic disease, patients comorbid with malignant tumors or severe organ dysfunction, patients comorbid with infectious diseases, patients with poor treatment compliance, and patients who were not interviewed.

Therapeutic methods

After their admission, the patients in both groups were administered oxygen inhalation, bedrest, and nutritional supplements. The maternal and fetal conditions were monitored closely.

In the CG, the patients were treated routinely. The patients were helped to avoid convulsions by the administration of appropriate antihypertensive drugs or magnesium sulfate (Minsheng Pharmaceutical Co., Ltd., Hangzhou, China). At the same time, any changes in a patient's vital signs were monitored closely. The health care workers needed to work actively and effectively. The patients were treated consecutively for 7 days.

In the RG, the patients were given aspirin combined with LMWH. First, the patients were instructed to take enteric-coated aspirin tablets (Zhongxin Pharmaceutical Co., Ltd., Beijing, China, H13023461) once a day/60 mg. At the same time, LMWH (Jiuyuan Genetic Engineering Co., Ltd., Hangzhou, China, H19990036) was combined with the aspirin treatment, once a day, with a subcutaneous injection of 4000 U each time. The patients were treated consecutively for 7 days.

Outcome measures

1. Clinical indicators: The blood pressure (SBP, DBP) was observed in both groups before and after the treatment.

2. Coagulation indexes: Before and after the treatment for one day, venous blood (5 mL) was drawn from the patients in both groups, centrifuged at 1500 × g and at 4°C for 10 min, and then stored in a freezer at -70°C for later use. The prothrombin times (PT), the activated partial thromboplastin times (APTT), and the fibrinogen (FIB) and D-dimer (D-D) levels were tested using the blood coagulation analyzer HF-6000.

3. Hemorheological indexes: Before and after the treatment for 2 weeks, the hematokrit and erythrocyte sedimentation rates were measured using an automatic hematology analyzer. Next, the plasma viscosity was measured using an automatic hemorheology analyzer.

4. Renal function indexes: Before and one day after the treatment, urine samples from the patients were collected in both groups. Then, venous blood (5 mL) was drawn from the patients in both groups, centrifuged at 1500 × g and 4°C for 10 min, and stored in a freezer at -70°C for later use. The 24-hour urinary protein quantification (24 h UP), the urea nitrogen (BUN), the blood uric acid (UA), and the serum creatinine (Scr) levels were measured using an automatic biochemical instrument.

5. Apgar scores [1]: The newborns were evaluated at 1 min and 5 min after their births, and scored from 0-10. The lower the score, the higher the risk of neonatal asphyxia.

6. Pregnancy outcomes: After the treatment, the incidences of fetal distress, neonatal death, postpartum hemorrhage, placental abruption, and fetal growth restriction were observed and recorded in both groups.

7. Efficacy: Markedly effective: After the treatment, the patients' clinical and coagulation indexes returned to normal, and the clinical symptoms disappeared. Effective: After the treatment, the patients' clinical indexes and coagulation indexes were improved, and their clinical symptoms basically disappeared. Ineffective: None of the symptoms changed after the therapy. Total effective rate = (markedly effective number + effective number)/total number × 100%.

Statistical analysis

SPSS 25.0 (Beijing Baiao Yijie Technology Co., Ltd., China) was used for the statistical analysis. GraphPad Prism 7 was used to generate the figures. The count data were represented as [n (%)] and compared by using Chi-square tests. When the theoretical frequency in a Chi-square test was less than 5, continuous correction Chi-square tests were used. The measurement data were represented as the means ± standard deviations (mean ± SD). Independent sample t-tests were used for the comparisons of the measurement data between the two groups. Paired T tests were used for the comparisons within groups before and after the treatment. A difference was statistically significant when $P < 0.05$.

Results

Baseline data

There was no significant difference between the RG and the CG in terms of their baseline data, such as average age, average gestational age, average parity, parturition experience, education background, diabetes history, drinking history, smoking history, place of residence, or diet ($P > 0.05$) (**Table 1**).

Comparison of the clinical indexes between the two groups before and after the therapy

Before the therapy, there was no significant difference in the SBP and DBP between the two groups ($P > 0.05$). After the therapy, the SBP and DBP in both groups were significantly lower than they were before the therapy ($P < 0.05$). After the therapy, SBP and DBP in the RG were significantly lower than they were in the CG, and the difference was statistically significant ($P < 0.05$) (**Table 2**).

Comparison of the coagulation indicators between the two groups before and after the therapy

There was no significant difference in the coagulation indexes between the two groups before the therapy ($P > 0.05$). After the treatment, the improvement in the coagulation indexes in both

Table 1. Baseline data of the patients in both groups [n (%), mean ± SD]

Factors	RG (n=54)	CG (n=50)	χ^2/t	P
Average age (years)	28.45±2.19	29.05±2.24	1.381	0.170
Average gestational age (weeks)	29.06±2.34	29.11±2.35	0.108	0.913
Average parity	1.76±0.15	1.81±0.17	1.593	0.114
Parturition experience			0.063	0.801
Primipara	30 (55.56)	29 (58.00)		
Multipara	24 (44.44)	21 (42.00)		
Educational background			1.233	0.266
Below high school	15 (27.78)	19 (38.00)		
High school or above	39 (72.22)	31 (62.00)		
Drinking history			1.248	0.263
No	18 (33.33)	22 (44.00)		
Yes	36 (66.67)	28 (56.00)		
Smoking history			0.419	0.517
No	25 (46.30)	20 (40.00)		
Yes	29 (53.70)	30 (60.00)		
Place of residence			0.396	0.529
Rural	26 (48.15)	21 (42.00)		
City	28 (51.85)	29 (58.00)		
Diet			0.025	0.873
Spicy	24 (44.44)	23 (46.00)		
Light	30 (55.56)	27 (54.00)		

Table 2. Comparison of the clinical indexes between the two groups before and after the therapy (mean ± SD)

Group	N	Systolic blood pressure (mmHg)		Diastolic blood pressure (mmHg)	
		Before treatment	After treatment	Before treatment	After treatment
RG	54	151.83±15.02	127.35±12.47	97.46±9.28	83.41±8.07
CG	50	152.97±15.06	133.25±13.05	98.11±9.24	93.15±9.01
t	-	0.386	2.357	0.357	5.815
P	-	0.700	0.020	0.721	< 0.001

groups was significantly better than it was before the therapy (P < 0.05). The PT and APTT in the RG were significantly higher than they were in the CG, and the FIB and D-D were significantly lower than they were in the CG. The differences were statistically significant (P < 0.05) (**Table 3**).

Comparison of the hemorheological indexes between the two groups before and after the therapy

There was no significant difference in the hemorheological indexes between the two groups before the therapy (P > 0.05). After the treatment, the hemorheological indexes in both groups were declined in different degrees compared with their levels before the therapy (P < 0.05). The hematokrit, erythrocyte sedimentation rate, and plasma viscosity in the RG were significantly lower than they were in the CG. The differences were statistically significant (P < 0.05) (**Table 4**).

Comparison of the renal function indexes between the two groups before and after the therapy

There was no significant difference in the renal function indexes between the two groups before the therapy. After the treatment, the improvement in the renal function indexes in both groups was significantly lower than it was before therapy. The 24 h UP, BUN, UA, and Scr levels in the RG were significantly lower than they were in the CG. The differences were statistically significant (P < 0.05) (**Figure 1**).

Comparison of the fetuses' Apgar scores between the two groups at the different time points after delivery

After delivery, the fetal scores were analyzed in both groups. The Apgar scores of the newborns in the RG were significantly higher than they were in the CG at 1 min and 5 min after the births. The differences were statistically significant (P < 0.05) (**Figure 2**).

Comparison of the pregnancy outcomes between the two groups after the therapy

After the therapy, the incidences of total adverse pregnancy outcomes in the RG were significantly lower than they were in the CG. The

Table 3. Comparison of coagulation indicators between the two groups before and after the therapy (mean ± SD)

Group	n	PT (s)		APTT (s)		FIB (g/L)		D-D (mg/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
RG	54	11.57±1.05	15.62±1.04	31.28±3.08	37.15±3.14	5.19±0.24	3.27±0.15	3.01±0.15	2.01±0.14
CG	50	11.81±1.08	13.89±1.18	32.07±3.04	34.75±3.16	5.14±0.28	5.68±0.28	2.99±0.17	3.25±0.16
t	-	1.149	7.945	1.315	3.883	0.979	55.270	0.637	42.140
P	-	0.253	< 0.001	0.191	0.001	0.329	< 0.001	0.525	< 0.001

Table 4. Comparison of the hemorheological indexes between the two groups before and after the therapy (mean ± SD)

Grouping	n	Hematokrit (%)		Erythrocyte sedimentation rate (mm/h)		Plasma viscosity (mpa·s)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
RG	54	38.16±3.04	25.16±2.11	28.23±2.19	15.23±1.08	2.45±2.08	1.28±1.02
CG	50	38.25±3.01	32.54±3.05	28.54±2.24	21.84±2.04	2.42±2.01	1.76±1.06
t	-	0.151	14.440	0.713	20.870	0.074	0.353
P	-	0.879	< 0.001	0.477	< 0.001	0.941	0.021

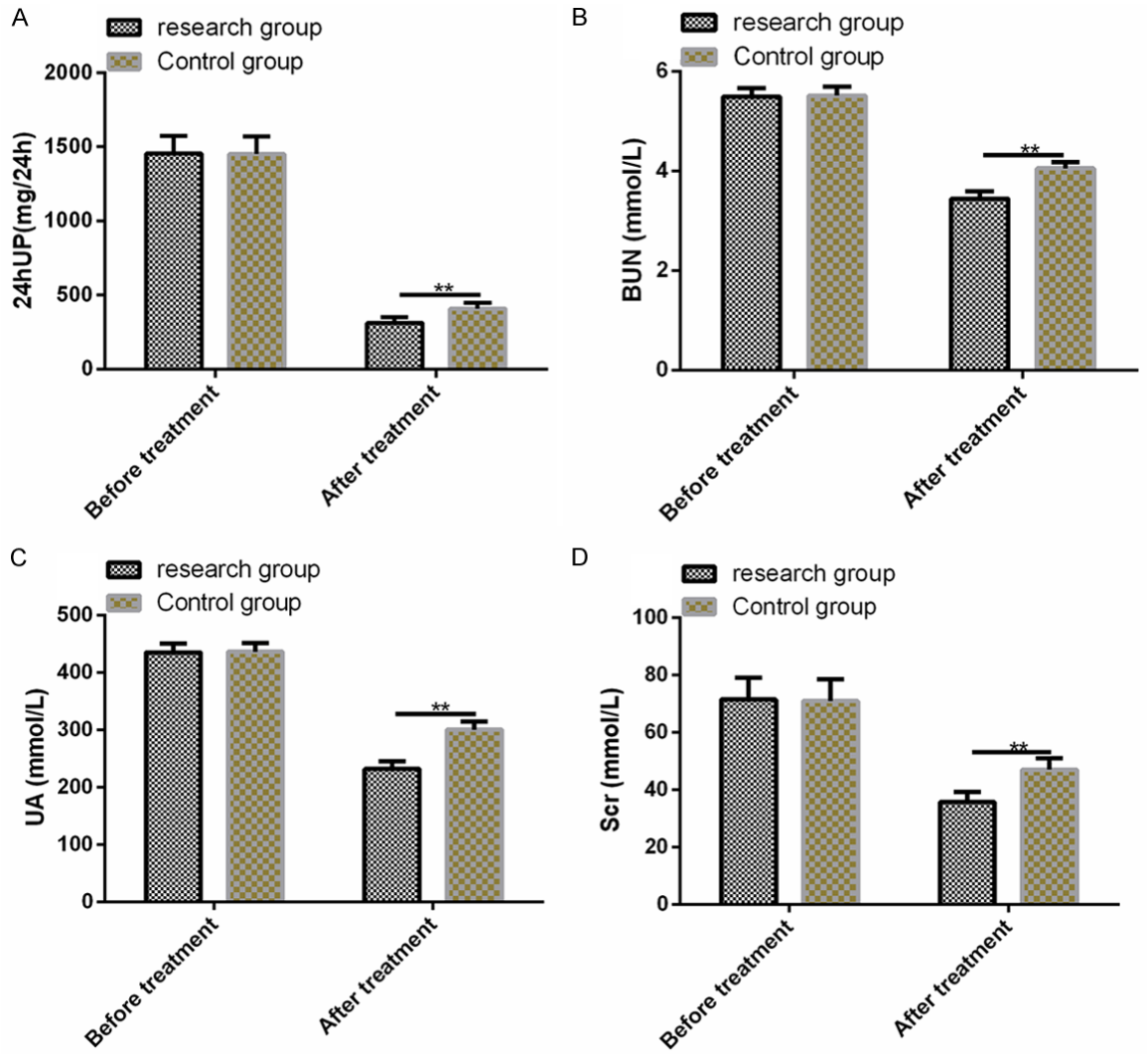

Figure 1. Comparison of renal function indexes between the two groups before and after the therapy. A: Before the treatment, there was no difference in the 24 h UP between the two groups. After the treatment, the 24 h UP levels in the RG were significantly lower they were in the CG. B: Before the treatment, there was no difference in the BUN between the two groups. After the treatment, the BUN level in the RG was significantly lower than it was in the CG. C: Before the treatment, there was no difference in the UA between the two groups. After the treatment, the level of UA in the RG was significantly lower than it was in the CG. D: Before the treatment, there was no difference in the Scr level between the two groups. After the treatment, the Scr level in the RG was significantly lower than it was in the CG. Note: Compared with before the treatment, $^{*}P < 0.05$; Compared with CG after the treatment, $^{**}P < 0.01$.

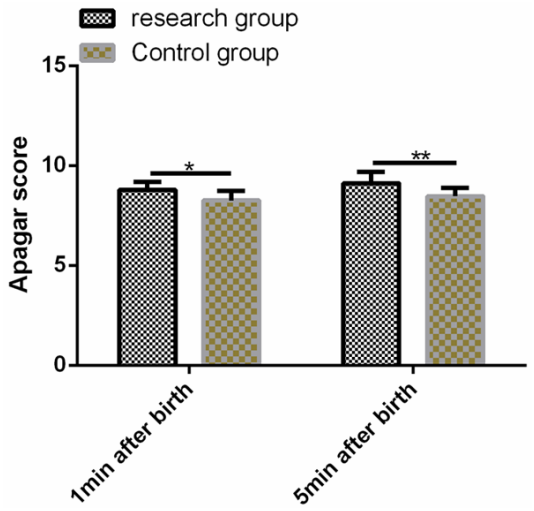

Figure 2. Comparison of the fetuses' Apgar scores between the two groups at the different time after delivery. The Apgar scores of the newborns in the RG were significantly higher than they were in the CG at 1 min and 5 min after the births. Note: Compared with the two groups, $^{*}P < 0.05$; Compared with the Apgar scores at one minute after the births, $^{**}P < 0.01$.

differences were statistically significant ($P < 0.05$) (**Table 5**).

Comparison of total effective rates between the two groups after the therapy

After the treatment, the total effective rate was 94.44% in the RG and 76.00% in the CG. The comparison revealed that the total effective rate of the patients in the RG after the treatment was significantly higher than it was in the CG, and the difference was statistically significant ($P < 0.05$) (**Table 6**).

Discussion

The pathogenesis of severe eclampsia is unclear, and its main feature is vasospasms [15]. Due to the damage to the corresponding vascular endothelial cells, uterine and placental thrombosis gradually gradually form [16], resulting in a hypercoagulable state for a long time and in abnormal coagulation function [17]. Studies have shown that preeclampsia carries risks of serious complications, and it is also associated with adverse pregnancy outcomes [18].

In this research, aspirin combined with LMWH was used to treat patients with severe preeclampsia, and it was found that the patients' pregnancy outcomes were significantly ameliorated after the therapy, and the treatment had a better curative effect. Studies have shown that oral enteric aspirin can improve blood pressure variability in patients with hypertension [19]. This is similar to the results of this research. The results revealed that the SBP and DBP of the patients in the RG were lower than they were in the CG after the therapy, indicating that aspirin combined with LMWH can effectively improve the blood pressure of severe preeclampsia patients, which may be because the combination of the two can better improve the thrombus. Aspirin can inhibit the activity of fatty acid oxidase, thus antagonizing platelet aggregation and activation, improving hemorheology, and relieving patients' hypercoagulable states [20]. LMWH has strong activity of anticoagulant factor Xa, which can prevent platelet aggregation by promoting the release of the plasminogen activator from the endothelium, thus improving the microcirculation of the body [21]. This is similar to the results of this study. The results revealed that the PT and APTT in the RG were significantly higher than they were in the CG, while FIB and D-D were significantly lower than they were in the CG after the treatment, indicating that aspirin combined with LMWH can effectively improve the hypercoagulable state of patients with severe preeclampsia, promote fibrinolytic activity, and play antithrombotic and anticoagulant roles. After the treatment, the hematocrit, erythrocyte sedimentation rate, and plasma viscosity in the RG were significantly lower than they were in the CG, which just showed that the

Table 5. Comparison of the pregnancy outcomes between the two groups after the therapy [n (%)]

Group	n	Normal pregnancy outcomes	Abnormal pregnancy outcomes					
			Fetal distress	Neonatal death	Postpartum hemorrhage	Placental abruption	Fetal growth restriction	Total
RG	54	50 (92.59)	0 (0.00)	0 (0.00)	1 (1.85)	2 (3.70)	1 (1.85)	4 (7.41)
CG	50	39 (78.00)	1 (2.00)	1 (2.00)	2 (4.00)	4 (8.00)	3 (6.00)	11 (22.00)
χ^2	-	4.479	1.090	1.090	0.427	0.881	1.208	4.479
P	-	0.034	0.296	0.296	0.513	0.347	0.271	0.034

Table 6. Comparison of total effective rates between the two groups after the therapy [n (%)]

Group	n	Markedly effective	Effective	Ineffective	Total effective rate
RG	54	39 (72.22)	12 (22.22)	3 (5.56)	51 (94.44)
CG	50	18 (36.00)	20 (40.00)	12 (24.00)	38 (76.00)
χ^2	-	-	-	-	7.156
P	-	-	-	-	0.007

combination of the two drugs can further reduce the blood viscosity, decrease the blood flow resistance, and improve the hemorheology.

Patients with severe preeclampsia often also suffer from significant proteinuria [22], so the kidneys can be seriously damaged, and determining the renal function levels is also a reliable means of measuring the pre-eclampsia conditions [23]. By comparing the level of renal function indexes in both groups before and after the therapy, this study found that the 24 h UP, BUN, UA, and Scr levels in the RG were significantly lower than they were in the CG after the treatment intervention. In the studies by Zhang et al., the intervention using LMWH for the preeclampsia patients was able to protect the kidney function of the patients and improve the fetal health [24]. This is similar to this research, suggesting that aspirin combined with LMWH can effectively reduce patients' renal function injuries, and it is also an intuitionistic result of optimizing severe preeclampsia. For now, the Apgar score is used clinically to evaluate whether newborns have asphyxia after birth [25]. The results of this study revealed that the Apgar scores of the newborns in the RG were significantly higher than they were in the CG at 1 min and 5 min after their births, indicating that the intervention of aspirin combined with LMWH can not only ameliorate patients' hypercoagulable state and hemorheology, but it can also promote an increase of placental blood perfusion, thus avoiding the lack of nutrition and oxygen intake in placental tissue and reducing the risk of fetal asphyxia. Studies have revealed that aspirin can reduce pregnant women's health risks, and LMWH can prevent fetal growth restrictions [26]. The results of this research revealed that the incidences of fetal distress, neonatal death, postpartum hemorrhage, placental abruption, fetal growth restriction, and adverse pregnancy outcomes in the RG were significantly lower than they were in the CG after the therapy, indicating that aspirin combined with LMWH can give full play to the advantages of different drugs and make their respective advantages complementary to each other, so it helps to ameliorate patients' pregnancy outcomes and promote the health of mothers and infants. After the therapy, the total effective rate of the patients in the RG was significantly higher than it was in the CG, indicating that the combination of aspirin and LMWH can improve patients' coagulation functions, clinical efficacy, and pregnancy outcomes, and with a higher level of safety.

Although this study has shown that aspirin combined with LMWH can bring better benefits to patients with severe preeclampsia, there is still room for improvement in this research. For example, we can further analyze the risk factors affecting the recovery of patients with severe preeclampsia, which will help nurses to identify which risk factors need additional attention. In the future, we will gradually carry out supplementary research from the above perspectives.

To sum up, aspirin combined with LMWH can effectively improve the clinical efficacy, the coagulation function, the renal function, and the blood pressure levels, and it can reduce the

adverse pregnancy outcomes in patients with severe preeclampsia.

Acknowledgements

This study was financially supported by a grant called Mitochondrial tRNA mutations associated with type 2 diabetes mellitus and gestational diabetes mellitus (2020JQ-938).

Disclosure of conflict of interest

None.

Address correspondence to: Yanchuan Li, Obstetrics, Shaanxi Provincial People's Hospital, 256 Youyi West Road, Xi'an 710068, Shaanxi Province, China. Tel: +86-15349261565; E-mail: liyanchuan2008@163.com

References

[1] Belay Tolu L, Yigezu E, Urgie T and Feyissa GT. Maternal and perinatal outcome of preeclampsia without severe feature among pregnant women managed at a tertiary referral hospital in urban Ethiopia. PLoS One 2020; 15: e0230638.

[2] Agarwal A, Goyal M, Jain J and Agarwal A. Congenital perisylvian syndrome presenting as post-partum seizures with preeclampsia. J Assoc Physicians India 2017; 65: 103-105.

[3] Lee JH, Zhang G, Harvey S and Nakagawa K. Temporal trends of hospitalization, mortality, and financial impact related to preeclampsia with severe features in Hawai'i and the United States. Hawaii J Health Soc Welf 2019; 78: 252-257.

[4] Haram K, Mortensen JH, Mastrolia SA and Erez O. Disseminated intravascular coagulation in the HELLP syndrome: how much do we really know? J Matern Fetal Neonatal Med 2017; 30: 779-788.

[5] Burr NE, Hull MA and Subramanian V. Does aspirin or non-aspirin non-steroidal anti-inflammatory drug use prevent colorectal cancer in inflammatory bowel disease? World J Gastroenterol 2016; 22: 3679-3686.

[6] Chime SA, Akpa PA, Ugwuanyi CC and Attama AA. Anti-inflammatory and gastroprotective properties of aspirin - entrapped solid lipid microparticles. Recent Pat Inflamm Allergy Drug Discov 2020; 14: 78-88.

[7] Kim IS, Yoo DH, Jung IH, Lim S, Jeong JJ, Kim KA, Bae ON, Yoo HH and Kim DH. Reduced metabolic activity of gut microbiota by antibiotics can potentiate the antithrombotic effect of aspirin. Biochem Pharmacol 2016; 122: 72-79.

[8] Huang J, Chen X, Xing H, Chen L, Xie Z, He S, Wang X, Li Y, Cui H and Chen J. Aspirin and heparin for the prevention of pre-eclampsia: protocol for a systematic review and network meta-analysis. BMJ Open 2019; 9: e026920.

[9] Poterucha TJ, Libby P and Goldhaber SZ. More than an anticoagulant: do heparins have direct anti-inflammatory effects? Thromb Haemost 2017; 117: 437-444.

[10] Pritchard ER, Murillo JR Jr, Putney D and Hobaugh EC. Single-center, retrospective evaluation of safety and efficacy of direct oral anticoagulants versus low-molecular-weight heparin and vitamin K antagonist in patients with cancer. J Oncol Pharm Pract 2019; 25: 52-59.

[11] Xu M, Xue W, Ma Z, Bai J and Wu S. Resveratrol reduces the incidence of portal vein system thrombosis after splenectomy in a rat fibrosis model. Oxid Med Cell Longev 2016; 2016: 7453849.

[12] Yang XL, Chen F, Yang XY, Du GH and Xu Y. Efficacy of low-molecular-weight heparin on the outcomes of in vitro fertilization/intracytoplasmic sperm injection pregnancy in non-thrombophilic women: a meta-analysis. Acta Obstet Gynecol Scand 2018; 97: 1061-1072.

[13] Rodger MA, Gris JC, de Vries JIP, Martinelli I, Rey E, Schleussner E, Middeldorp S, Kaaja R, Langlois NJ, Ramsay T, Mallick R, Bates SM, Abheiden CNH, Perna A, Petroff D, de Jong P, van Hoorn ME, Bezemer PD and Mayhew AD; Low-Molecular-Weight Heparin for Placenta-Mediated Pregnancy Complications Study Group. Low-molecular-weight heparin and recurrent placenta-mediated pregnancy complications: a meta-analysis of individual patient data from randomised controlled trials. Lancet 2016; 388: 2629-2641.

[14] Poon LC, Shennan A, Hyett JA, Kapur A, Hadar E, Divakar H, McAuliffe F, da Silva Costa F, von Dadelszen P, McIntyre HD, Kihara AB, Di Renzo GC, Romero R, D'Alton M, Berghella V, Nicolaides KH and Hod M. The International Federation of Gynecology and Obstetrics (FIGO) initiative on pre-eclampsia: a pragmatic guide for first-trimester screening and prevention. Int J Gynaecol Obstet 2019; 145 Suppl 1: 1-33.

[15] Vangrieken P, Al-Nasiry S, Janssen GMJ, Weseler AR, Spaanderman ME, Bast A and Schiffers PMH. The direct and sustained consequences of severe placental hypoxia on vascular contractility. PLoS One 2018; 13: e0202648.

[16] Tannetta DS, Hunt K, Jones CI, Davidson N, Coxon CH, Ferguson D, Redman CW, Gibbins JM, Sargent IL and Tucker KL. Syncytiotrophoblast extracellular vesicles from pre-eclampsia placentas differentially affect platelet function. PLoS One 2015; 10: e0142538.

[17] Hu Y, Yan R, Zhang C, Zhou Z, Liu M, Wang C, Zhang H, Dong L, Zhou T, Wu Y, Dong N and Wu Q. High-mobility group box 1 from hypoxic trophoblasts promotes endothelial microparticle production and thrombophilia in preeclampsia. Arterioscler Thromb Vasc Biol 2018; 38: 1381-1391.

[18] Venkatesh KK, Strauss RA, Westreich DJ, Thorp JM, Stamilio DM and Grantz KL. Adverse maternal and neonatal outcomes among women with preeclampsia with severe features < 34 weeks gestation with versus without comorbidity. Pregnancy Hypertens 2020; 20: 75-82.

[19] Ji AL, Chen WW and Huang WJ. Clinical study on influences of enteric coated aspirin on blood pressure and blood pressure variability. Eur Rev Med Pharmacol Sci 2016; 20: 5017-5020.

[20] Shen DS, Yang YJ, Kong XJ, Ma N, Liu XW, Li SH, Jiao ZH, Qin Z, Huang MZ and Li JY. Aspirin eugenol ester inhibits agonist-induced platelet aggregation in vitro by regulating PI3K/Akt, MAPK and Sirt 1/CD40L pathways. Eur J Pharmacol 2019; 852: 1-13.

[21] Diaz JA, Wrobleski SK, Alvarado CM, Hawley AE, Doornbos NK, Lester PA, Lowe SE, Gabriel JE, Roelofs KJ, Henke PK, Schaub RG, Wakefield TW and Myers DD Jr. P-selectin inhibition therapeutically promotes thrombus resolution and prevents vein wall fibrosis better than enoxaparin and an inhibitor to von Willebrand factor. Arterioscler Thromb Vasc Biol 2015; 35: 829-837.

[22] Dong X, Gou W, Li C, Wu M, Han Z, Li X and Chen Q. Proteinuria in preeclampsia: not essential to diagnosis but related to disease severity and fetal outcomes. Pregnancy Hypertens 2017; 8: 60-64.

[23] Kucukgoz Gulec U, Sucu M, Ozgunen FT, Buyukkurt S, Guzel AB and Paydas S. Spot urine protein-to-creatinine ratio to predict the magnitude of 24-hour total proteinuria in preeclampsia of varying severity. J Obstet Gynaecol Can 2017; 39: 854-860.

[24] Zhang Y, Liu F, Chen S and Zhong M. Low-molecular-weight heparin protects kidney through an anti-apoptotic mechanism in a rat preeclamptic model. Eur J Obstet Gynecol Reprod Biol 2015; 188: 51-55.

[25] Razaz N, Cnattingius S and Joseph KS. Association between Apgar scores of 7 to 9 and neonatal mortality and morbidity: population based cohort study of term infants in Sweden. BMJ 2019; 365: l1656.

[26] Groom KM and David AL. The role of aspirin, heparin, and other interventions in the prevention and treatment of fetal growth restriction. Am J Obstet Gynecol 2018; 218: S829-S840.