Effect of Shexiang baoxin pills on clopidogrel resistance in patients with acute coronary syndrome

Li Zhang, Na Liu, Jinying Zhang* and Hui Zhang
Department of Cardiology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Abstract: **T**o explore the effect of Shexiang baoxin pills on clopidogrel resistance in patients with acute coronary syndrome (ACS). 131 cases with ACS combining with clopidogrel resistance admitted to our hospital during March 2013 to November 2015 were recruited in this study and were divided into observation group (66 cases) and control group (65 cases) according to the random number table method. And the patients in observation group were given clopidogrel with Shexiang baoxin pills therapy while the control group clopidogrel therapy to observe the platelet aggregation rate, heart rate variability (HRV), and serum level of matrix metalloproteinase-2 (MMP-2). After treatment, the platelet aggregation rate in observation group was significantly less than the group before treatment and that of control group ($P<0.05$); And before treatment, the serum level of MMP-2 and HRV of the two groups were not statistically significant ($P>0.05$). But after treatment, the serum level of MMP-2 and HRV of the observation group were significantly lower and better respectively than the observation group before treatment and control group ($P<0.05$). Shexiang baoxin pill plays an active role in reducing clopidogrel resistance in patients with ACS, lowering platelet aggregation rate and serum level of MMP-2, improving HRV in the body.

Keywords: Shexiang baoxin pill, acute coronary syndrome, clopidogrel resistance, influence.

INTRODUCTIOIN

With the development of society and the speed up of social aging process, the incidence of the coronary heart disease (CHD) is becoming more and more. Therefore, it is of significance to take effective therapies to improve the life quality of patients with CHD. Currently, Percutaneous Coronary Intervention (PCI) is the main method to treat the patients with Acute Coronary syndrome (ACS) (Zhou LJ, 2015). And aspirin with clopidogrel is required during the therapeutic period, with the main side effect of antiplatelet agent resistance. And only after clopidogrel is activated by CytochromeP450 in the liver, can it plays a role in inhibiting platelet aggregation. And clopidogrel resistance has become one of the clinical issues. And in this study, Shexiang Baoxin Pills were given to patients with ACS to interfere the clopidogrel resistance.

METERIALS AND METHODS

General information

131 cases with ACS combining with clopidogrel resistance in our hospital during March 2013 to November 2015 were recruited in this study. And the patients who developed Acute ST-segment elevation ACS and were against the drugs given in this study would not be included. And all the included patients were divided into observation group (with 66 cases) and control group (with 65 cases) according to the random number table method. And in the observation group, there were 31 male patients and 34 female patients, 51-74 years old (an average of 62.11±8.37 years), 35 cases combined with hypertension and 27 cases diabetes; while in the control group, there were 31 male patients and 33 female patients, 51-73 years old (an average of 62.04±8.22 years), 33 cases combined with hypertension and 28 cases diabetes. And it had no statistically significance in the gender and age between two groups ($P>0.05$), therefore, the two groups were comparable.

Dosage regimen

The patients in observation group were given clopidogrel and Shexiang Baoxin Pills with the specification--oral clopidogrel, 75mg/d and four pills each time, 3 times/d. While the control group were only given clopidogrel with specification of oral clopidogrel, 75mg/d.

Observational indexes

The observational indexes included platelet aggregation rate, platelet inhibition rate, heart rate variation (HRV) and serum level of MMP-2. And the platelet inhibition rate refers to the difference between the platelet aggregation rate before and after treatment.

STATISTICAL ANALYSIS

SPSS 19.0 software was used to analyze data statistics in this study, mean standard deviation (x±s) and percentage (%) were used to express the measuring results and the counting results, and T-test and chi-square test (χ^2) were used to check the findings, and $P<0.05$ was statistically significant.

*Corresponding author: e-mail: e-mail:Jinyingzhang119@sina.com

Table 1: Comparison of platelet aggregation rate between the two groups

Groups	Cases	Platelet aggregation rate before treatment	Platelet aggregation rate after treatment	Platelet aggregation rate
Observation group	66	28.39±4.78	21.29±2.88	10.88±1.58
Control group	65	28.46±3.94	28.59±4.76	8.87±1.54

Table 2: Comparison of the serum level of MMP-2 between two groups

Groups	Cases	Before treatment	After treatment
Observation group	66	55.42±8.33	39.13±5.48*
Control group	65	56.12±7.91	45.97±4.88

Table 3: Comparison of the HRV between the two groups

Groups	Cases	time	SNDD (ms)	SDANN (ms)	rMSSD (ms)	PNN50 (%)	VLF (ms^2)	LF(ms^2)	HF (ms^2)	LF/HF
Observation group	66	before treatment	47.01±5.88	27.98±5.66	19.01±5.62	2.88±1.02	657.29±88.24	331.98±90.01	160.88±24.31	2.48±0.99
		After treatment	95.21±9.24*Δ	45.92±8.72* Δ	36.96±8.33* Δ	4.82±3.25* Δ	240.85±82.13* Δ	196.84±96.15* Δ	160.35±12.54	1.18±0.09* Δ
Control group	65	before treatment	47.21±8.33	26.88±5.21	19.01±8.88	3.39±2.88	666.89±102.35	353.28±95.18	159.86±10.52	2.08±0.44
		After treatment	48.01±9.45	28.98±3.22	18.88±5.67	3.09±1.58	938.46±122.87	344.88±90.66	164.99±12.34	2.29±0.33

Note: *compared with the control group, P<0.05; △compared with the same group before treatment, P<0.05.

SNDD: Standard Diviation of NN intervals
SDANN: The Standar Deviation of the Averages of the N-N intervals
rMSSD: Root Mean Square of Successive Differences
PNN50: The Percent of Successive Normal Interbeat Intervals greater than 50 msec
VLF: Ultra-low-frequency
LF: Low Frequency
HF: High Frequency

RESULTS

Comparison of platelet aggregation rate

After treatment, the platelet aggregation rate of the observation group were significantly less than the group before treatment (P<0.05); and it was still obviously less when compared with the control group (P<0.05). Seen in table 1.

Comparison of serum level of MMP-2 between the two groups

Before treatment, the serum level of MMP-2 of the two groups were not statistically significant (P>0.05); After treatment, the serum level of

MMP-2 of the observation group was much lower than the control group and the observation group before treatment (P< 0.05). As shown in table 2.

Comparison of the HRV between the two groups

Before treatment, the HRV of the two groups were not statistically significant (P>0.05); After treatment, HRV of the observational group was much better than the observation group before treatment and control group (P<0.05) as shown in table 3.

DISCUSSION

Clopidogrel, as a new type of thiophene pyridine derivatives, has a strong influence on inhibiting platelet activity. And it has this function only after taking orally and dose not play an active role *in vitro* (Xiao M *et al*, 2014; Zhao W *et al*, 2015; Huang XH *et al*, 2013; Tang JN *et al*, 2015). And the clopidogrel resistance will be generated (Lv JR *et al*, 2013; Yang GL *et al*, 2014; Ren ZL *et al*, 2013; Wang SH *et al*, 2013; Chen J *et al*, 2013). And it is of significant importance to explore one effective measure to lowering clopidogrel resistance in the patients with ACS.

ACS is a kind of serious cardiovascular disease, belongs to one of the severe types of CHD (Tian L, 2013). And ACS is mainly induced by the rupture and invasion of the coronary atherosclerosis (Dehghani MR *et al*, 2014). Among them, MMP-2 plays an important role in the degradation of extra cellular matrix. And the change of serum level of MMP-2 can reflect the pathological development of the body. There are many researches on Shexiang Baoxin Pills in treating ACS but less on MMP-2. And the findings in this study showed that serum level

of MMP-2 in the observation group was much higher than the control group ($P<0.05$), indicating that Shexiang Baoxin Pills can inhabit the generation of MMP-2 factors, helping for controlling the rupture of the vulnerable plaque and further development of the disease.

Shexiang Baoxin Pills is a kind of Chinese patent medicine, with good function in improving myocardial ischemia (Xie LQ *et al*, 2014). And the medicine is mainly consists of musk, ginseng, borneol, bezoar, styrax, toad venom, cinnamon, etc. and has a good effect of relieving chest stuffiness. Chinese medicine pharmacology holds the idea that Shexiang Baoxin Pills can expand coronary artery, bring better blood flow and has good effect of lowering platelet aggregation, improving inflammatory response in the body (Lv HC *et al*, 2014; Jia SM, 2014). And styrax and borneol are the commonly used drugs to promote blood circulation and remove meridian obstruction, and Ginseng can improve heart rate. The mechanism of Shexiang Baoxin Pills in treating patients with ACS is that musk extract has good effect of expanding blood vessels, and can protect vascular endothelial cells, enhancing the activity of the NO synthetase in the arterial wall, reducing the generation of oxygen free radicals. And this medicine can reduce the occurrence rate of angina pectoris and improve the ST-T electrocardiogram of the patients (Zhou LJ, 2014; Peng QD *et al*, 2014). The findings in this paper showed that there was a remarkable effect of Shexiang Baoxin Pills on reducing platelet aggregation rate and the serum level of MMP-2 and improving HRV.

CONCLUSION

Shexiang Baoxin Pills plays an active role in lowering clopidogrel resistance, platelet aggregation rate and the serum level of MMP-2, platelet inhibition rate and improving HRV and in patients with ACS. But its specific mechanism still remains to be further studied.

This paper is supported by the Science and Technology Talents Team Construction Program of Zhengzhou City-Science and Technology Talents (131PLJRC670) and the Science and Technology Research Projects of Henan Province (13A320623).

REFERENCES

Zhou LJ (2015). Clinical curative effect observation of Shexiang Baoxin Pills in the patients with acute coronary syndrome. *Journal of Eastern Liaoning University (Natural Sciences),* **21**(01): 66-68.

Xiao M, Hao EG and Liu YS (2014). Effect of the combined application of Naoxintong capsule and Clopidogrel on the platelet aggregation in the patients with acute coronary syndrome. *Liaoning Journal of Traditional Chinese Medicine,* **41**(12): 2619-2621.

Zhao W, Sun SH and Qiu GB (2015). Effect of Clopidogrel on the phosphorylation of the platelet in the patients after percutaneous coronary intervention. *International Journal of Laboratory Medicine,* **36**(01): 42-44.

Huang XH, Chen Y and Tang Y *et al* (2013). Analysis of the relative factors causing Clopidogrel resistance in the patients with Acute Coronary Syndrome after percutaneous coronary intervention. *Journal of Chinese Practical Diagnosis and Therapy,* **27**(12): 1153-1155.

Tang JN, Shen L and Liu CL *et al* (2015). Plasma Levels of C1q/TNF-Related Protein 1 and Interleukin 6 in Patients With Acute Coronary Syndrome or Stable Angina Pectoris. *Am. J. Med. Sci.,* **349**(2): 130-136.

Lv JR, Shen ZJ and Wang YJ *et al* (2013). Research on gene polymorphism of the CYP2C19 and traditional Chinese medical syndrome typing distribution in the 117 patients with Acute Coronary Syndrome. *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease,* **11**(12): 1427-1429.

Yang GL, Wan SP and Zhou HX *et al* (2014). Effect of Shexiang baoxin pills on the platelet aggrevaiation in the patients with acute myocardial infarction. *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease,* **12**(01): 8-9.

Ren ZL and Li R (2013). Effect of clopidogrel with various degrees on the platelet aggrevaiation in the patients with acute coronary syndrome. *Molecular Cardiology of China,* **13**(02): 477-480.

Wang SH, Wang YH and Zhang H (2013). Progress in the mechanism of Clopidogrel resistance. *International Journal of Laboratory Medicine,* **34**(07): 843-846.

Chen J, Lu YM and Huang DM *et al* (2013). Analysis of the relative factors causing Clopidogrel resistance in the patients with Acute Coronary Syndrome after percutaneous coronary intervention. *Chinese Journal of cardiovascular Rehabilitation Medicine,* **22**(02): 176-179.

Tian L (2013). Effect of early application of Clopidogrel with loading dose on the activity and parameter of blood platelet in the patients with acute coronary syndrome. *Hebei. Medicine,* **19**(08):1137-1140.

Dehghani MR, Taghipour-Sani L and Rezaei Y *et al* (2014). Diagnostic importance of admission platelet volume indices in patients with acute chest pain suggesting acute coronary syndrome. *Indian Heart J,* **66**(6): 622-628.

Xie LQ, Huang H and Chen W *et al* (2014). Combined application of high-loading-dose of Clopidogrel and Tirofiban Hydrochloride in the patients with Non-ST Elevation Acute Coronary Syndrome. *Progress in Modern Biomedicine,* **14**(27): 5307-5310.

Lv HC, Wu HY and Ge JB (2014). Please include this title as per format of PJPS. *Journal of Dalian Medical University,* **36**(04): 387-392.

Jia SM (2014). Application of Shexiang baoxin Pills in 23 cases with Non-ST Elevation Acute Coronary

Syndrome. *Chinese Journal of Integrative Medicine on Cardio-/Cerebrovascular Disease,* **12**(10): 1204-1205.

Zhou LJ (2014). Effect of Shexiang baoxin Pills on MMP-2 expression in the patients with Acute Coronary Syndrome. *Journal of Eastern Liaoning University (Natural Sciences),* **20**(04): 300-302.

Peng QD, Yang SY and Peng XL *et al* (2014). Effect of Shexiang baoxin Pills on exercise tolerance in the patients with acute coronary syndrome. *The Journal of Medical Theory and Practice,* **27**(19): 2558-2559.