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Full Length Research Paper

Effects of different combinations of prescription of invigorate blood and diffuse Bì formula on myocardial protection of hyperlipidemia rats with isoproterenol-induced ischemic injury

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This research aimed at observing the effects of different combinations of prescription of invigorate blood and diffuse Bì formula (IBDB) on resisting myocardial ischemic injury and adjusting blood lipid to seek for the best combination for IBDB. The research used the model of hyperlipidemia rats with isoproterenol-induced myocardial ischemic injury and treated by gavage with 8 different combinations of IBDB using orthogonal design to observe the effects of different combinations on electrocardiogram (ECG), heart function, Superoxide dismutase (SOD), malondialdehyde (MDA) and total antioxidation capacity (T-AOC) of serum and myocardium and blood lipid of acute ischemia and thus find out the best combination with mathematical method. The result indicated that different combinations of IBDB could protect ischemic myocardium and the heart function of rats and directly work against myocardial injury and adjust blood lipid at different levels. Comparison between all treated groups suggests that the 7th, 6th and 3rd combinations are superior than the 4th and 5th in improving ECG (P<0.05) and the 7th and 8th are superior than the 1st in improving FS (P<0.05), the 2nd is superior than the 5th and 7th in increasing SOD of serum (P<0.05), the 7th combination is superior in decreasing MDA of serum and myocardium and every combination except the 8th can reduce CHO without significant difference. Through the comparison of prescription effects, it is found out that Combination 7 is the best for IBDB.

Key words: Invigorate blood and diffuse Bì formula, combination, myocardial ischemic injury, selection from direct comparison, Traditional Chinese Medicine.

INTRODUCTION

The main treatment for Traditional Chinese Medicine (TCM) is to use the prescription of herbs with varieties of combinations, the core of which is the combination of herbs (Gao et al., 2006). Research on a new TCM prescription is to choose proper herbs and determine the dose and proportion of each herb. Herbs are chosen according to the classic TCM books and the prescription of clinical treatment nowadays (Wang et al., 2001). Combination such as the dose and proportion of each herb is usually determined by the researcher itself and lacks of objectivity and accuracy. It is a better solution to determine the prescription with mathematical method by observing the effects of different combinations. This research takes the example of invigorate blood and diffuse Bì formula (IBDB), which is the treatment for coronary artery disease, to learn about the effects of the combinations with different Chinese herbs extracts of IBDB on ISO-induced acute myocardial injury of hyperlipidemia rats and find out the best combination. Coronary artery disease is one of the most serious

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diseases around the world which endanger human health and cardiovascular disease is on the top of the list of causes for population death in China, half of which is caused by coronary artery disease (NCCD, 2009). TCM prescription suggests fair curative effects during clinical treatment for coronary artery diseases (Wang et al., 2008). Based on the prescription of currently used in clinical treatment (Xiong, 2010; Wang, 2010; Gu et al., 2005), we finally figured out the herbs for IBDB.

For this research, we use extracts of herbs instead of decoction pieces to assure the stability of efficacy. TCM has features of targeted therapy and holistic regulation and we could infer from the TCM theory of combination of disease-syndrome that IBDB can work for both anti-myocardial injury and blood lipid adjustment and thus choose corresponding animal model and observation indexes.

MATERIALS AND METHODS

Plant extracts

IBDB formula consists of extract of *Radix et Rhizoma Salviae Miltiorrhizae* (Danshen) (EDS), extract of *Fructus Trichosanthis* (Gualou) and *Bulbus Allii Macrostemonis* (Xiebai) (EGX), extract of *Radix Astmgali* (Huangqi) (EHQ), extract of *Radix Ophiopogonis* (Maidong) (EMD) and extract of *Radix Paeoniae Rubra* (Chishao) (ECS):

EDS: batch No. 20100203, Salvianolic acid B≥60%.
EGX: batch No. 20101009, total saponins≥1.0%, adenosine≥0.07%.
EHQ: batch No. 20100928, Calycosin-7-glucoside≥0.08%, total flavonoids≥0.17%, Astragaloside IV≥0.09%, Astragalosides≥2%, Astragalus polysaccharides≥0.5%.
EMD: batch No. 20100926, total saponins≥0.8%, total polysaccharides≥40.50%.
ECS: batch No. 20100927, Paeoniflorin≥58.2%.

All extracts above were provided by Medicine Research Laboratory of Guang'anmen Hospital. The voucher specimens were deposited in our laboratory for future reference. When dispensing, all extracts were mixed according to the designed proportion and made into suspension with required concentration using 0.5% CMC-Na.

Reagents and drugs

Superoxide dismutase (SOD) Kit, Malondialdehyde (MDA) Kit and total antioxidation capacity (T-AOC) Kit were all purchased from Nanjing Jiancheng Bioengineering Inst. Isoproterenol (batch No. 018k5003) a product of Sigma Chemicals Co. Chloral hydrate (batch No. 20100111) was purchased from Sinopharm Chemical Reagent Co. Ltd.

Animals

140 male adult Wistar rats (SPF grade) weighing 190-220 g each were used in the study. All animals were provided by Vital River Lab Animal Technology Co. Ltd. Approval certification was SCXK (Beijing) 2006-0009. All rats were housed in an air-conditioned room with controlled temperature of 22±2°C and relative humidity of 55±15%. All animals were acclimated 5 days and allowed free access to standard food and water before they were used. The animal experiments in the study followed the European Community guidelines for the use of experimental animals and were approved by the Animal Care Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences.

Modelling method

This experiment used the combination model of hyperlipidemia rats model and ISO-induced myocardial injury rats model.

Hyperlipidemia rats' model

Rats were continuously fed with high fat diet (including 78.8% basic forage, 1% cholesterol, 10% yolk powder, 10% lard and 0.2% bile salt) for 15 days and randomly given Four Items of Blood-lipid Tests (CHO,TG, HDL-L, LDL-L) to certify blood lipid increase thus the model was established.

ISO-induced myocardial injury rats model

After the hyperlipidemia rats model was established, rats were given subcutaneous multiple injection with ISO, 10 ml/kg each time, once a day for 2 days and after final injection given ECG detection to prove myocardial ischemia thus the model was established.

Animal grouping, administration and treatment

Animal grouping and administration

According to TCM composition theory**,** active extracts as EDS,EGX, EHQ, EMD and ECS, which had been preliminary screened out *in vitro*, were divided into 5 component factors and 2 dose levels were chosen for each of the five extracts according to clinical treatment experience and all combinations were grouped into eight (Table 1). Finally rats were divided into normal group, hyperlipidemia group (HLP group), model group and eight groups for different combinations (11 groups in total), 10 to 20 rats for each group. We kept feeding normal diet to normal group. Normal group, HLP group and model group were fed with equal 0.5% CMC-Na by gavage and different tested combinations to other eight groups. Four items of blood lipid tests (CHO, TG, HDL-L, LDL-L) were detected on the 15^{th} day and the results of HLP group, model group and 8 groups for different combinations were compared with normal group to prove that blood lipid increased evidently ($P < 0.05$), and the establishment of the hyperlipidemia rats model were certified. On the 16^{th} and 17^{th} days, we injected ISO to induce myocardial injury and detect ECG result right after the second injection showed acute myocardial change and the myocardial ischemia was proved by a raised Point J and Wave T, and the ISO-induced myocardial injury model was established. The sampling and all kinds of index detections were conducted after 72 h, which is the 20^{th} day.

On the 20^{th} day, the rats in every group were weighed and numbered and got intraperitoneal anesthesia of 10% chloral hydrate (350 ml/kg) and were prepared for echocardiography. The blood sample was taken from abdominal aortic and the serum was collected in two tubes separately. The rats' chests were opened and hearts were removed and cleaned in 4% saline and dried. Part of the hearts was for pathology and fixed in 4% paraformaldehyde. Part of the left ventricular of other hearts was cut and mixed with saline with a weight-to-volume ratio of 1:9 to make homogenate. Serum and homogenate of myocardium were centrifuged at 3000 r/min and 4°C to collect the upper clean water.

Index measurement

Echocardiographic examination

Examined by Visualsonics Vevo 770 system. SOD, MDA and

Table 1. Animal grouping and administration.

Factor	n	1	2	3	4	5
		EDS g/kg	EGX g/kg	EHQ g/kg	EMD g/kg	ECS g/kg
No.1	13	0.1	0.75	0.25	0.75	0.05
No.2	12	0.1	0.75	0.25	0.5	0.075
No.3	13	0.1	1.25	0.375	0.75	0.05
No.4	12	0.1	1.25	0.375	0.5	0.075
No.5	13	0.15	0.75	0.375	0.75	0.075
No.6	12	0.15	0.75	0.375	0.5	0.05
No.7	13	0.15	1.25	0.25	0.75	0.075
No.8	12	0.15	1.25	0.25	0.5	0.05

Table 2. Effects of ISO injection on the ECG.

Groups	n	Point J (mV)
Normal	10	0.053±0.035**
HLP	10	0.071±0.014**
Model	20	0.241±0.026##
No.1	13	0.205±0.017##*
No.2	12	0.199±0.023##*
No.3	13	0.183±0.014##**
No.4	12	0.232±0.028##
No.5	13	0.217±0.024##*
No.6	12	0.181±0.032##**
No.7	13	0.177±0.015##**
No.8	12	0.193±0.023##**

*P<0.05, **P<0.01 vs. model group; #P<0.05, ##P<0.01 vs. HLP group.

T-AOC measurement was determined with spectrophotometer in biochemical method according to the introduction of kits provided by Nanjing Jiancheng Bioengineering Inst. Four Items of blood lipid (CHO, TG, HDL-L and LDL-L) were measured by German Roche Modnlar automatic analyzer. Pathological sectioning of heart cardiac apex was sampled and fixed in 4% paraformaldehyde and processed with HE staining to observe the change of pathomorphology.

Statistics

All data collected were expressed by mean±SE (±s) and analyzed with SPSS16.0 by one-way ANOVA. LSD method was adopted during regular variance, but Tamhane analysis (T2) of variance was adopted during irregular variance.

RESULTS

Effects of ISO injection on the ECG of hyperlipidemia rats

After the injection of ISO, ECG of rats indicted of myocardial ischemia by raised Point J and Wave T, showing serious myocardial ischemic injury. Groups treated with prescription showed a smaller deviation than model groups ($P<0.05$ or $p<0.01$). Among the groups treated with prescription, the 7th, 6th and 3rd groups were superior to others. Among the groups, the 7th combination was superior to the 1st ($p=0.028$), the 4th ($p=0.01$) and the 5th ($p=0.011$) and the 6th and 3rd combinations were superior to the 4th and 5th ($p<0.05$) (Table 2).

Effects on heart function of hyperlipidemia rats

Compared with HLP group, EF and FS of model group declined significantly ($P<0.01$); compared with model group, EF and FS of the 2nd, 4th, 7th and 8th combination increased significantly ($P<0.05$). Among groups treated with prescriptions, there was no significant difference of EF between all groups and the FS value of the 7th and 8th combination was higher than the 1st combination ($P<0.05$) (Table 3).

Effects on MDA, SOD and T-AOC of serum and myocardium

Compared with normal group and HLP group, MDA value of serum and myocardium of the model group rose significantly and SOD of serum and myocardium and T-AOC of serum dropped significantly ($P<0.05$ or $P<0.01$) (Tables 4 and 5).

Among groups treated with prescription, SOD of serum for the 2nd combination was higher than the 5th ($P=0.014$) and 7th ($P=0.018$) and there was no significant statistical difference between other combinations; MDA of serum for the 7th and 8th combinations was lower than that of the 1st combination ($P<0.05$) and there was no significant statistical difference between other combinations; there was no different between SOD values of myocardium for each group ($p>0.05$); MDA of myocardium for the 7th

Table 3. Effects on heart function.

Groups	n	EF (%)	FS (%)
Normal	10	89.49±5.46**	45.77±7.42**
HLP	10	90.14±7.12**	47.51±7.59**
Model	8	66.73±4.01	32.77±4.85
No.1	10	70.34±7.38	33.53±3.00
No.2	8	75.87±9.89*	39.83±6.20*
No.3	9	74.18±7.90	36.69±4.68
No.4	8	75.49±5.73*	38.95±5.30*
No.5	10	74.49±4.68	37.21±3.69
No.6	6	74.02±8.02	35.28±1.84
No.7	8	78.07±6.78*	40.18±4.94*
No.8	9	76.68±8.60*	40.00±3.72*

*P<0.05, **P<0.01 vs. model group.

Table 4. Effects on MDA, SOD and T-AOC of serum.

Groups	n	SOD (u/ml)	MDA (nmol/ml)	T-AOC (u/ml)
Normal	10	230.33±22.03**	1.43±0.91**	18.91±2.05
HLP	10	232.31±27.87**	1.96±1.36*	17.54±5.00
Model	8	202.94±31.00	4.67±3.58	14.24±3.66
No.1	10	250.38±29.21**	2.84±1.64	16.21±3.29
No.2	8	260.73±19.45**	2.41±1.71*	16.23±3.40
No.3	9	251.78±20.89**	2.64±1.71	15.13±5.30
No.4	8	248.23±20.22**	2.06±1.24*	16.29±2.63
No.5	10	228.39±25.78	2.37±1.43*	15.36±2.82
No.6	6	240.90±17.84*	2.38±1.09	15.29±4.44
No.7	8	232.69±9.29*	1.68±1.71**	16.07±1.97
No.8	9	249.96±12.47**	1.67±1.15**	15.43±0.96

*P<0.05, **P<0.01 vs. model group.

combinations; there was no different between T-AOC values of myocardium for each group ($p > 0.05$).

Effects on four items of blood lipid test (CHO, TG, HDL-L and LDL-L)

Compared with model group, CHO of rats in groups treated with IBDB decreased significantly ($P < 0.05$ or $P < 0.01$), while there was no significant statistical difference for TG ($P > 0.05$).

Difference among the group was not significant ($P > 0.05$). Compared with model group, there was no significant statistical difference for HDL-L and LDL-L (Tables 6 and 7).

Observation of paraffin section and HE staining

Morphology of normal cells has complete structure and tidiness arrangement, while myocardium cells of model group were in disorder with inflammatory cell infiltration and collagen sedimentary and fibroblasts hyperplasia, minimal necrosis, swollen fracture of muscle fiber and interstitial edema, the 1st and 7th combinations showed the most remarkable improvement (Figure 1).

DISCUSSION

To decide the best combination for IBDB, it is important to reflect and stabilize the effect. In the study, there were two changes made on the base of traditional TCM pharmacology. Firstly, herb prescription is a combination of decoction pieces by their function according to TCM theory (Yu, 2004), but since active ingredients in Chinese medicine are complex, effects are unstable if directly treating with herb combinations or simply-processed decoction pieces. Therefore, we use extracts instead of decoction pieces in this research. A potential prospect of TCM research is to use Chinese medicinal herbs as

Table 5. Effects on MDA, SOD and T-AOC of myocardium.

Groups	n	SOD (u/mgprot)	MDA (nmol/mgprot)	T-AOC (u/gprot)
Normal	10	21.25±4.09	0.86±0.25**	16.22±4.27*
HLP	10	23.78±4.08*	1.33±0.41*	17.11±3.98**
Model	8	18.12±3.16	1.86±0.58	9.82±5.43
No.1	10	24.25±3.42**	1.21±0.54**	15.42±6.51*
No.2	8	22.71±4.12	1.03±0.33**	15.46±4.18*
No.3	9	21.72±4.12	1.29±0.44**	16.65±2.27**
No.4	8	22.71±2.76	1.20±0.19**	18.71±4.32**
No.5	10	23.74±3.41*	1.35±0.25*	18.55±3.40**
No.6	6	23.57±4.36	1.10±0.58**	16.37±4.45*
No.7	8	24.03±2.58*	1.02±0.23**	19.62±5.16**
No.8	9	23.22±7.56	1.48±0.27	16.78±3.84**

*P<0.05, **P<0.01 vs. model group.

Table 6. Effects on CHO and TG in serum.

Groups	n	CHO	TG
Normal	10	1.68±0.18**	0.88±0.28
HLP	10	3.06±0.57	1.20±0.47
Model	8	3.12±0.57	0.93±0.21
No.1	10	2.47±0.37**	0.86±0.23
No.2	8	2.22±0.28**	0.89±0.25
No.3	9	2.43±0.33**	0.82±0.28
No.4	8	2.35±0.10**	0.83±0.15
No.5	10	2.40±0.17**	0.93±0.23
No.6	6	2.44±0.33*	1.12±0.26
No.7	8	2.44±0.39*	1.08±0.29
No.8	9	2.54±0.32	0.88±0.43

*P<0.05, **P<0.01 vs. model group.

Table 7. Effects on HDL-L and LDL-L in serum.

Groups	n	HDL-L	LDL-L
Normal	10	1.03±0.11	0.49±0.06**
HLP	10	1.15±0.23	0.95±0.27
Model	8	1.06±0.11	0.91±0.19
No.1	10	1.10±0.09	1.01±0.24
No.2	8	1.12±0.11	0.79±0.16
No.3	9	1.12±0.15	1.02±0.18
No.4	8	1.13±0.04	0.89±0.12
No.5	10	1.22±0.10	0.85±0.09
No.6	6	1.12±0.06	0.87±0.24
No.7	8	1.11±0.13	0.93±0.23
No.8	9	1.15±0.20	1.04±0.20

*P<0.05, **P<0.01 vs. model group.

library of natural compounds and filter active compound through proper method (Normile, 2003). The research on extracts of Chinese medicinal herbs is a key step to find active ingredients in Chinese medicine and clarify the effective mechanism of Chinese medicine and its prescriptions. Secondly, different from chemicals with single target, TCM extract compound has features of targeted therapy and holistic regulation. Referring to TCM Disease-Syndrome theory, IBDB can invigorate blood and diffuse Bì and replenish Qì and remove phlegm and cure Phlegm-Blood stasis syndrome of coronary artery diseases, therefore we believe direct treatment target of IBDB is anti-myocardial ischemia while it adjust lipid metabolism. ISO-induced non-specific infarct myocardial necrosis is an ideal model for myocardial ischemic and anoxic injury (Rona et al., 1959; Jia et al., 2006), which has similar pathological character and mechanism of myocardial necrosis with human. That's why we choose hyperlipidemia rats with ISO-induced acute myocardial ischemic injury model.

Research of pharmacology suggest that each extract of IBDB has certain efficacy, such as Salvianolic Acids for anti-oxidant and scavenging free radicals and improving myocardial microcirculation (Yu and Zhang, 1994; Li et al., 2009; Wang, 2010), ethanol extracts of *Fructus Trichosanthis* and *Bulbus Allii Macrostemonis* for extending coronary vessels and anti-myocardial anoxic injury and adjustment of blood lipid (Cao et al., 2001; Sun et al., 2004), Astragalosides and Astragalus polysaccharides for improving myocardial metabolism and reducing myocardium calcium overload to adjust oxidative system and minimize oxidative injury of myocardial ischemia (Feng et al., 2006; Wang, 2010), Paeoniflorin for decreasing coronary resistance to improve myocardium blood and adjust and improve heart function (Liu et al., 2007), extract of *Radix Ophiopogonis* for increasing nutrition blood flow of cardiac muscle and anti-myocardial ischemia (Cheng, 2001; Zhuo et al., 2003). When all kinds of extracts work together, combined effect (that is, superposition, collaboration, antagonism and independence) becomes the key factor

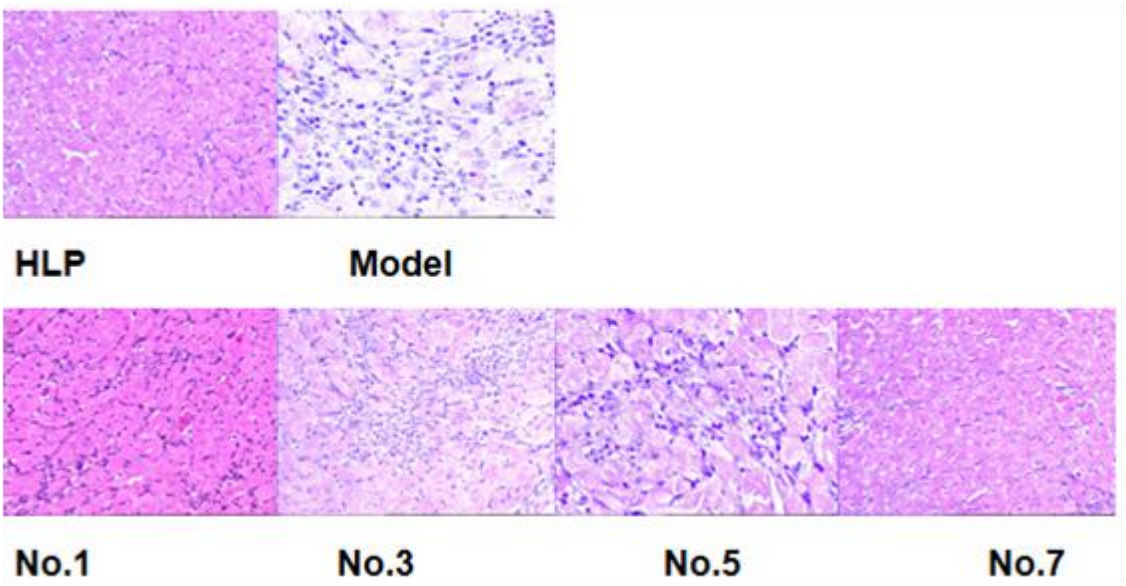

Figure 1. Myocardium HE×40.

of efficacy. In the view of over-all situation, all combinations of IBDB can protect heart function of rats and myocardial ischemic injury and scavenge free radicals efficiently and inhibit lipid per oxidation to protect ischemic myocardium thus directly resist myocardial injury with overall adjustment for blood lipid and decrease CHO. Efficacy of different combinations of IBDB changes with different proportion and dose of each herb.

Comparison between all treated groups in this research suggests that the 7^{th}, 6^{th} and 3^{rd} combinations are superior in improving ECG of acute myocardial injury and the 7^{th} and 8^{th} combinations are superior in protecting heart function when acute injury, the 2^{nd} combination is superior in increasing SOD of serum, the 7^{th} combination is superior in decreasing MDA of serum and myocardium and every combination except the 8^{th} can reduce CHO without significant difference. Thus, direct comparison shows the 7^{th} combination (proportion of extracts of 3: 25: 5: 15: 1, and dose, Table 1) is the best combination for IBDB, which is also suggested by simple pathological observation. Results for this research commonly agree on superior combination in multi-index comparison. However, the result is exceptive while it's more common to have different superior combination for different index, which implies difficulty in applying the direct comparison. Meanwhile, only 8 different combinations are involved in this research, which are the exclusive options for superior combination, though maybe the optimal combination is not among these combinations. For reasons already enumerated, we use orthogonal design in experimental design and will conduct further research on mathematical multi-target optimization. Therefore this research will lay a foundation for seeking for the best IBDB combination in mathematical modelling method.

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