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Research Article

A Twin-Herbal Combination was found to have Cardio-Vascular Protection Effects after repeated RCTs on four groups of patients with Different Disease Background A Cross-Biostatical Study

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Abstract

Background and Objective: To perform an integrated Cross-Biostatical analysis of four randomized controlled trials (RCTs) to assess the efficacy and safety of oral administration of D&G capsule (D&G) for the maintenance of cardiovascular health.

Methods: Data from the populations of four completed RCTs were pooled for this integrated Cross-Biostatical analysis. Mean changes from baseline in IMT and lipid profile were the main lines of attention; treatment differences were compared between D&G and Placebo groups. Primary outcome was Carotid artery intima-media thickness (IMT). Secondary outcome was the lipid profile. Analyses included primary and secondary outcome measures repeated at individual time points.

Results: The pooled RCT data involved 453 subjects (245 D&G; 208 Placebo); demographic characteristics were similar between treatment groups. Taking all 4 groups together, the mean improvements in IMT from baseline to week 24 were 0.9163 to 0.8939 in D&G group, and 0.8997 to 0.8964 in Placebo group. A statistically significant improvement after treatment was observed (P <0.001) in D&G group, not in Placebo group.

Conclusion: The integrated analysis of the pooled biostatic data further confirmed the efficacy and safety of D&G in the vascular protection effects.

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Introduction

Aging has become a worldwide public health problem. One of the most threatening concern is related to cardio-vascular health, as age related deteriorations of the heart and peripheral arteries progressively lead to circulatory hazards of varying severities [1]. In the most serious situations, coronary or cerebral obstruction could lead to cardiac or cerebral ischemic disasters. In more gradual affections, selective and regional morbidities could result [2,3].

As the risk factors leading to cardiovascular hazards have become better known and well defined, energetic explorations, including surgical and pharmaceutical means to prevent the hazards have started. Successful surgical stentings of obstructed arteries have led to preventive enlargements for even early obstructions. On the pharmaceutical side, it seems that statin control of vascular endothelial cholesterol deposits has remained the only reliable means.

Marzilli in 2012 discussed about the causative factors of atherosclerosis, which involves the complicated microenvironment of the endothelium of the artery. Apart from simple cholesterol deposits, other conditions like the inflammatory state; antioxidant and muscular relaxation states etc. are all contributing towards the progressive deterioration. A logical deduction from Marzilli's "solar system theory" might be that the ideal form of prevention of arteriosclerosis is one that would maintain an multiple targets, all-round favorable microenvironment [4]. Marzilli's logical deduction should have invited serious exploration on the use of medicinal agents that possibly provide the multiple cardiovascular protective effects [5].

Herbal medicine of traditional chinese medicine origin

Many medicinal herbs have been used in Traditional Chinese Medicine (TCM) as supportive agents to maintain cardiovascular health, which has been interpreted as "circulatory strength". We had a thorough study of relevant literature and decided to select one simple twin-herb formula to be used as a standard supplement to maintain cardiovascular health. One component of the formula viz. *salvia miltiorrhiza* belongs to a most frequently used herb for the same purpose and in the past decades, have been studied extensively in the laboratory with proven effects on endothelial deposits, smooth muscle relaxation and anti-inflammation etc [6]. To match this most popular cardiovascular protective agent, a less popular medicinal herb best known for its anti-inflammatory effects was selected to make the twin formulae [7].

This innovative twin preparation was repeatedly tested in the laboratory to confirm its basic vascular protective effects before its application in clinical trials. Four groups of patients with different orientations of cardiovascular deterioration had been selected for separate clinical trials, using the same twin formula since 2001, at intervals of 3-4 years. The four selected groups of patients with different clinical problems included:

- ✓ Coronary artery disease [8,9]
- ✓ Diabetics' with hypertension [10,11]
- ✓ Postmenopausal and syndrome [12] and
- ✓ Peripheral vascular disease [13].

Methods

Integrated analysis of the four clinical trials using pooled biostatics data

The design of the trials was kept standard and the only one serving team remained uniform throughout. The twin-herb formula in the fixed herbal ratio was prepared as capsules by a reputable manufacturer and the essential features of the Clinical Trials are presented as follows:

Design of trials: double-blind, randomized, placebo-controlled trials (RCTs) [14,15].

Objectives: to assess the efficacy and safety of a Herbal Formula D&G Capsule (twin-herb formula) for the maintenance of cardiovascular health.

Method: Trials were similar in design. Patient populations are shown in Table 1. Individual patient data were pooled; a repeated analysis of covariance was performed in the intent-to-treat (ITT) population.

Data illustrated that the four separate clinical trials on four different group of patients with different clinical backgounds did show good uniformity in age, dosage and duration of treatment.

All RCTs were approved by the Clinical Research Ethics Committee (CREC) and all patients provided written informed consent.

Study herbal formula

The raw herbs (ratio 7:3 by weight) of D&G capsule were prepared, authenticated, and extracted according to the standards of good manufacturing practice (GMP) at the Hong Kong Institute of Biotechnology (HKIB). The prepared D&G

Table 1: Details of the four randomized, double-blind, placebo-controlled clinical trials.

Disease Background	Trial date	Daily drug dose	Number of patients	Duration	Sex, men/women	Mean age, years
I. Coronary Obstruction	2001-2005	3 g /day	100	24 weeks	87/13	58
II. Diabetes with Hypertension	2005-2008	1g/day, 2g/day	90	24 weeks	67/23	55
III. Menopausal with border lieu hypertension	2009-2012	1g/day	165	48 weeks	0/165	56
IV. Peripheral vascular disease	2015-2017	3g/day	98	24 weeks	73/25	67

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herbs were aqueous-extracted (herb–water ratio of 1:10) at 100°C two times for 60 minutes, and once for 30 minutes, sprayed dried at -660mm Hg and 50–600C, and the dried powder was encapsulated (500mg/capsule).

Patient populations

In total, 453 male and female patients, aged 36 to 85 years, were included in the integrated analysis; 100 patients age 40–70 years, with angiographically documented coronary artery disease (>50% reduction in luminal diameter CAD) in at least one vessel and stable angina status participated in Trial I; 90 patients with essential hypertension (SBP 160/90mmHg before treatment)participated in Trial II; 165 patients aged 45—65 years, menstruation stopped for more than 12 months, and fasting serum LDL ≥ 3.5 mmol/L, without taking hormones, statins ornutritional supplements participated in Trial III and 98 patients with known Peripheral Arterial Disease (PAD) participated in Trial IV.

Inclusion criteria

Angiographically documented coronary artery disease (Trial I)

Established essential hypertension (Trial II)

Postmenopausal women (Trial III)

Symptoms of intermittent claudications (Trial IV)

Exclusion criteria (for all groups)

Unstable angina

Renal insufficiency

Bleeding disorders

Hepatic or gastrointestinal diseases

Severe ischaemic ECG changes,

Fasting serum glucose > 7.0 mmol/L,

Creatinine > 100 umol/L, or

Triglyceride > 11.3 mmol/L

Maintenance on Warfarin

All patients were informed of the details of the entire study, including the purpose, procedures, data collection methods, test articles, risks, potential adverse effects, rescue measures, and confidentiality.

Outcome measures

Carotid artery Intima-Media Thickness (IMT) was taken as the primary outcome. Secondary outcome included the lipid profile (TC, TG, LDL and HDL).

Statistical analysis

Data were analyzed using the SPSS software (version 25.00, SPSS Inc.). IMT was the primary outcome measure of treatment efficacy and used for the pooled analysis. The efficacy analysis was based on changes in IMT in the pooled population, using longitudinal analysis to incorporate information in the 4 trials. The Integrated Change from Baseline in IMT and lipid profiles were analyzed with an ANCOVA, with factor of age as a covariate. Changes within one treatment group were assessed by using paired t-test. Significance level was defined as $\alpha = 0.05$.

Results of pooled data analysis

Results from the four different clinical trials had been separately analyzed and every trial had been shown significant improvements in the primary and secondary outcomes. In order to gain more credibility of the trial results, we believe pooling the data in a cross biostatistical analysis would be indicated.

Analyses were based on individual patient data from Case Report Forms (CRFs), assembled into a data set for the pooled population. This provides a comparison that avoids some limitations inherent to clinical trials. Importantly, these analyses provide an overview of the clinical evidence related to the safety and effectiveness of the Herbal Formula D&G Capsule.

Demographics and disposition

The baseline (before treatment) status of the 4 different groups of patients showed their great similarity which supports the cross-data biostatistical analysis Table 2.

Analysis of overall efficacy

Results indicated that IMT was significantly improved in D&G group after treatment ($p<0.001$), while, there no significant changes were observed in Placebo group after treatment (Table 3, Figure 1). ITM could be conveniently pooled to illustrate different groups with uniform responses.

Table 3 gives detailed data of changes in IMT in the pooled D&G and placebo groups. TC, HDL and LDL were also significantly decreased in both groups ($p<0.05$), but TG in the placebo group was significantly increased at the end of study ($p<0.05$).

There was no change of the blood sugar level in both groups throughout the study period.

Table 2: Baseline Characteristics of Pooled Population from 4 RCTs (N=453).

Parameter	D&G (n=245)	Placebo (n=208)	P value
Age(yrs)	58.2 ± 8.3	59.4 ± 8.4	0.140
Sex: Male Female	 124 121	 103 105	0.817
IMT (mm)	0.915 ± 0.362	0.899 ± 0.282	0.615
TC (mmol/l)	5.34 ± 1.19	5.30 ± 1.19	0.693
TG (mmol/l)	1.62 ± 1.18	1.60 ± 1.05	0.855
HDL (mmol/l)	1.45 ± 0.38	1.43 ± 0.38	0.533
LDL (mmol/l)	3.19 ± 1.08	3.19 ± 1.02	0.995
Glucose (mmol/l)	5.77 ± 1.88	5.63 ± 1.35	0.429

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Table 3: Ultimal changes in IMT and other parameters after 24 weeks' treatment as are shown in the pooled data.

Parameter	D&G (n=245)		Placebo (n=208)	
	Baseline	Post-treatment	Baseline	Post-treatment
IMT (mm)	0.9163 ± 0.3657	0.8939 ± 0.3540***	0.8997 ± 0.2826	0.8964 ± 0.2732
TC (mmol/l)	5.35 ± 1.19	5.15 ± 1.10***	5.30 ± 1.20	5.17 ± 1.17**
TG (mmol/l)	1.60 ± 1.20	1.59 ± 1.08	1.56 ± 1.00	1.71 ± 1.31*
HDL (mmol/l)	1.45 ± 0.39	1.42 ± 0.36*	1.43 ± 0.39	1.40 ± 0.37*
LDL (mmol/l)	3.22 ± 1.10	3.06 ± 0.97***	3.22 ± 1.03	3.07 ± 1.07***
Glucose (mmol/l)	5.77 ± 1.94	5.70 ± 1.66	5.55 ± 1.13	5.5 3± 1.38

*p<0.05, **p<0.01, ***p<0.001 when compared with baseline

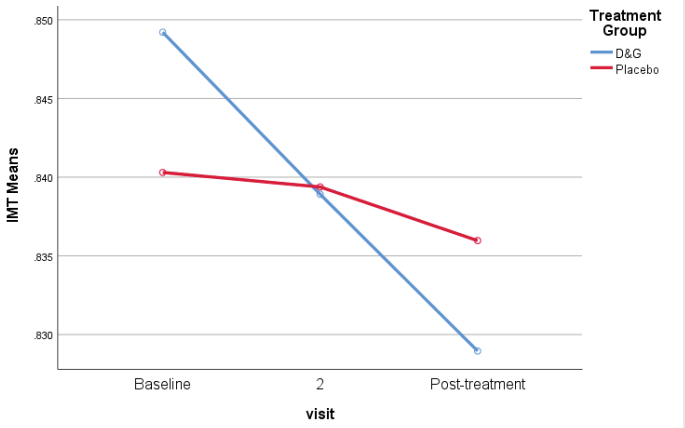

Figure 1: Changes of IMT at each visit with combined pooled data. .

Summation of IMT results of treatment (D&G) group and placebo group showing obvious superiority of treatment group.

Safety analysis

D&G herbal capsules were well tolerated in all groups. No significant adverse events were reported. Liver function and hematological profiles remained normal.

Discussion

Now that the risk factors leading to cardio-vascular hazards are thoroughly known, preventive measures accordingly have developed along a comprehensive direction. "Primary Level" prevention is the basic arrangement for patients known to be at high risk when cholesterol lowering therapy is the routine. "Secondary Prevention" refers to more targeted prophylaxis when a specific pathology like another coronary or cerebrovascular attack is to be expected. A more proactive preventive direction aims at the prevention of occurrence of the risk factors viz. hypertension, atherosclerosis, cholesterol and sugar levels, and is understood as "Primordial Prevention" [16-18].

Accumulation of statistical results in the past decades does indicate the successes of different forms of prevention [19,20]. However, it is clear that individual differences prevail: there are plenty of affected people not responding well to the preventive measures. More embarrassing disappointments occur when not only are the preventive measures against blood cholesterol not working perfectly but undesirable outcomes of coronary or cerebrovascular accidents still occur. Apart from more careful observations, apparently little can be offered to the disappointed group [21].

Genetic predisposition is widely accepted as the explanation to the failure of preventive measures with wide variations [22]. On the other hand, looking at the complexity of microenvironment leading to obstructive pathology of cardiovascular structures, one could also question: could the single target type of preventive treatment be over specific, good for one pathology (e.g. Cholesterol deposits) and yet not taking care of inflammation, spastic tendencies etc? [23,24].

Herbal medicine started in the old days as "Folk-forces". The thousands of years of practice has offered no scientific explanations apart from clinical observations. The "satisfactory" clinical applications have not been target (pathology) orientated but instead, aim at the acquisition of general well-being through holistic considerations. Since cardiovascular problems must have been affecting all human beings ever since history started, it is easy to identify favourable choices of supportive agents for cardiovascular problems.

When we started this research project in 2001, we carefully selected two widely used medicinal herbs in Traditional Chinese Medicine to form the twin herbs formula, with the aim of giving additional support to the prevention of cardiovascular hazards. We assumed that orthodox preventive therapies might be deficient and not very effective for some patients because the specific orientations might not be able to give comprehensive preventive effects. We assumed that the twin-herb formula could be taking care of more mis-matching problems leading to the cardiovascular hazards [25,26].

While we started planning the clinical trials for the efficacy of the twin-formula, we performed a series of laboratory experiments with the aim of showing multiple bioactivities of the formula, which should indirectly indicate its pharmacological effects.

The bioactivity studies included (i) Anti-inflammatory and anti-oxidative tests [27,28]; ii) Vascular protection tests [29,30]; iii) Myocardial effects [31,32]; and Genomic studies. Results of the bioactivity studies allowed us to speculate that the twin formula should be able to create a favorable microenvironment with good control of inflammatory activities in the promotion of an effective prevention program in a holistic direction [33, 34].

We chose four areas of major concern related to cardiovascular hazards viz. coronary obstruction, hypertension, perimenopause stress and peripheral arterial disease, for separate clinical trials under randomized control directions. The objectives were uniform and the major outcome measure was Intimal Medium Thickness (IMT), which is a well-accepted surrogate marker for the study of vascular deterioration. Uniformity of trial results could be expected. The blood lipid profile was selected as supportive outcome measures.

The individual clinical trials all showed positive effects of the twin formula. The pooled data of the four trials well

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supported the individual trials, thus further strengthening the data and it gives additional encouragement to the further development of the twin formula.

In the completed trials, patients on specific anti coagulants like Warfarin were excluded for fear of interference and safety. To continue a proper development of the twin formula, whether its application has significant disturbances to the routine vascular therapies needs careful studies [35].

We have performed limited investigation in the "herb-drug" interaction of the twin formula and common anti coagulants. A brief summary is given as follows.

The simultaneous administration of the twin formula and aspirin/ Warfarin to experimental rats showed that the metabolism of aspirin was not affected whereas the Warfarin pharmacokinetic and pharmacodynamics states showed significant interferences. The preliminary studies indicated that patients on Warfarin might avoid using this twin formula until more information is obtained [36,37].

Conclusion

We used a simple twin herb formula D&G as an evidence-based supplement to maintain the cardiovascular health of 4 groups of patients with different primary clinical problems in 4 separate randomized control trials. The results in the individual trials already showed very positive results as were exemplified in the IMT data and lipid profiles. We venture to pool the data together in a cross-biostatistical analysis with the openness to further testify with a bigger population. To our satisfaction, this exercise showed a consistent improvement with the D&G formula as had been shown in the previous individual clinical studies. Earlier, we have separately reported the treatment results of the four clinical trials together with extensive laboratory studies [38]. The present cross-biostatistical analysis would provide additional evidence.

D&G can be recommended as a safe supplement for the maintenance of cardiovascular health. Further studies to work out possible herb-drug interactions with many standard cardiac therapeutic agents would further guarantee its safety, efficacy and wider circulation.

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