Effects of Tanshinone on hyperandrogenism and qualitity of life in women with polycystic ovary syndrome: study design of a double-blind, placebo-controlled, randomized trial

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Abstracts: Polycystic ovary syndrome is one of the most common and confusing endocrine disorder in women. PCOS is characterized by hyperandrogenism , oligo/amenorrhea, and polycyctic ovary (PCO) morphology, which may be associated with insulin resistance and androgen excess. The prevalance of hyperandrogenism is 60%-80% in women of PCOS.PCOS is characterized by hyperandrogenism , oligo/amenorrhea, and polycyctic ovary (PCO) morphology, which may be associated with insulin resistance and androgen excess. The prevalance of hyperandrogenism is 60%-80% in women of PCOS. Tanshinones are a class of bioactive constituents isolated from Salvia miltiorrhiza. The significant advantages of CHM may be safe, effective, multi-targets and multiple methods for treating hyperandrogenism in PCOS.W e design a double-blind, placebo-controlled, randomized trial not only attest the clinical efficacy but also could provide Evidence of evidence-based medicine for the therapy of PCOS.

Key words:polycystic ovary syndrome, hyperandrogenism, randomized trial, protocol design.

Introduction

Polycystic ovary syndrome is one of the most common and confusing endocrine disorder in women. Prevalence rates of PCOS were highly variable with the use of different diagnostic criteria, and the rate is 18% according to the Rotterdam diagnostic criteria[1]. PCOS is characterized by hyperandrogenism, oligo/amenorrhea, and polycyctic ovary (PCO) morphology, which may be associated with insulin resistance and androgen excess. The prevalance of hyperandrogenism is 60%-80% in women of PCOS[2]. The major clinical and biochemical features of hyperandrogenism are hirsutism, acne, alopecia, seborrheic dermatitis, and abnormality sex steroid levels including elevated androstenedione, testosterone, dehydroepiandrosterone sulfate (DHEAS) levels, as well as decreased sex hormone binding globulin (SHBG) level. The syndrome presents with not only a reproductive manifestations but also a metabolic implications including insulin resistance, obesity, dyslipidemia, systemic inflammation, and type 2 diabetes[3-5].

The long-term therapy for women of PCOS who do not desire for pregnancy is still not yet uniform, depending on the specific clinical presentations and individualized patient goals. Comprehensive treatment methods for hyperandrogenism, glucose and lipid metabolic dysfunction include lifestyle modifications, diuretic medicine, insulin-sensitizing and anticholesteremic agent, as well as oral contraceptives[6]. Traditional Chinese Medicine(TCM) is an important part of complementary and alternative medicine (CAM). Chinese herbal medicine has been emerging as one of the commonly practiced medicines for PCOS[7]. Tanshinones are a class of bioactive constituents isolated from Salvia miltiorrhiza (Danshen) which is a common used herb in Traditional Chinese Medicine.

Cryptotanshinone (CT) is the major bioactive tanshinone in the plant and has several pharmacological effects including anti-inflammatory, anti-oxidative, anti-cholinesterase, anti-bacterial, antiplatelet aggregation and anti-cancer[8-10]. CHM has been used for the treatment of PCOS but the evidences for safety and efficacy are minimal. The animal experiment showed that cryptotanshinone can induce favorable alterations in androgen excess and insulin resistance as well as glucose metabolism[11]. There is still lack of scientific justification of clinical trial for the use of

tanshinone in women with PCOS. Particularly, a randomized controlled trial (RCT) has not been performed to evaluate the herbal medicine on hyperandrogenism, metabolic profiles and quality of life in women with PCOS who do not attempt to conceive.

With this study, we sought to explore the effects of tanshinone in women with PCOS who do not attempt to conceive and to explore whether tanshinone has positive effects on hyperandrogenism, quality of life, glucose and lipid metabolism.

2. Materials and methods

2.1 study design and ethnic

The study was approved by the Ethical Committee of First Affiliated Hospital of Heilongjiang University of Chinese Medicine (2010HZYLL-016). This is a multicentere, randomized, double blind and placebo-controlled clinical trial. Informed written consents will be obtained from all eligible women who participate in this study and will be randomized into either of the two groups (tanshinone capsules or placebo).

2.2 setting and recruitment

The study will be conducted in the outpatient of four hospitals in mainland China: First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Affiliated Hospital of Jiangxi college of Chinese Medicine, Huaian Maternal and Child Health Hospital, Lianyungang Maternal and Child Health Hospital.

2.3 participants

A total of 100 eligible patients will be recruited from four centers in China. All patients will examined by one of the clinical study gynecologist and will be enrolled into the trial according to the inclusion and exclusion criteria.

2.3.1 diagnostic Criteria

The diagnosis of PCOS for this study were confirmed according to the Androgen Excess Society criteria and all subjects must have hyperandrogenism (hirsutism and/or hyperandrogeniaemia), ovarian dysfunction (oligoanovulation and/or polycystic ovaries), and exclusion of other androgen excess related disorders. Oligomenorrhea is defined as an intermenstrual interval >35 days or <8 menstrual bleedings in the past year. Amenorrhea is defined as an intermenstrual interval >90 days. Clinical hyperandrogenism is defined as a Ferriman-Gallwey (FG) score ≥5 [12].

2.3.2 Inclusion criteria

The inclusion criteria for this study were as follows: (1) Adult female 18 to 35 years of age who have been diagnosed with PCOS ; (2) oligomenorrhoea/amenorrhoea ; (3) clinical or biochemical features of hyperandrogenism ; (4) With no desire of children by contraception within 6 month.

2.3.2 Exclusion criteria

The exclusion criteria were as follows: (1) Use of hormonal drugs or other medications, which could affect the results of the study expecially Chinese herbal prescriptions in the past 12 weeks ; (2) Patients with other androgen excess endocrine disorders including 21-hydroxylase deficiency, hyperprolactinemia, Cushing syndrome, severe insulin resistance,thyroid dysfunction ; (3) Patients with history of sever cardiac , pulmonary, hepatic, renal, neurologic disease or mental illness ; (4) Pregnancy or lactation.

2.4 Interventions

Eligible participants will be randomized into one of the two arms: Tanshinone capsules (1g, three times/ day) or placebo capsules. The tanshinone capsules (China State Food and Drug Administration (SFDA) approval no. Z13020110) and placebo both be provided by Hebei Xinglong Xili Pharmaceutical Co. LTD. They have the same outer packing, dosage, shape, and predominant flavor. Tanshinone or placebo will be administrated orally for 12 weeks. The main pharmaceutical formulation of tanshinone capsules is cryptotanshinone, which comprises 90 % of total formulation in the experimental drug.

2.5 Study specific visits and procedures

The trial phase: treatment with either tanshinone or placebo for 12 weeks. Participants will attend five times visits in total: screening visit (1 time), baseline visit(1 time), monthly visits (2 times), end of treatment visit (1 time). At baseline and on completion of 3 months, participants will undergo repeat measurements on test days to include a HCG stimulation test, a 75g 2h oral glucose tolerance test, a hyperinsulinemic euglycemic clamp clamp test and blood sample for assays of reproductive hormones, plasma glucose and lipid. Adverse events and drug co-treatments will be recorded during visits.

2.6 study assessment (include questionnairs)

2.6.1primary outcome

The primary outcome measure is a decrease of 10 ng/dl in basal testosterone.

2.6.2 secondary outcomes

(1) HCG induced response of androgens including 17-hydroxyprogesterone (17-OHP), androstenedione (A2), testosterone (T).

(2) Insulin resistance by the glucose disposal rate (GDR) with hyperinsulinemic euglycemic clamp test

(3) Reproductive hormones: testosterone (T), estradiol(E2), 17-α-hydroxyprogesterone (17-OHP), follicle stimulation hormone (FSH), leutinizing hormone (LH), sex hormone binding globulin (SHBG) and dehydoepiandrosterone sulphate (DHEAS).

(5) Fasting gluco-lipid metabolic profiles: fasting blood glucose, fasting insulin , C-peptide, glycosylated hemoglobin Alc(HbAlc), cholesterol, triglycerides (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C).

(6) Oral glucose tolerance test (OGTT): serum for glucose, Insulin and c-peptide levels will be determined.

(7) Weight, blood pressure, waist/hip circumference, F-G score and acne.

(8) Adverse events.

2.8 randomization and blindings

The randomization will be performed through a web-based randomization system operated by an independent data center (Institute of Basic Research of Clinical Medicine, China Academy of Chinese Medical Sciences, Beijing). Recruited Participants will be randomly and blindly assigned to tanshinone group (n=50) or placebo group (n=50) in a ratio of 1:1. The identification code and random number, which are unique for each participant, will be given by a web-based system (http://210.76.97.192:8080/dst/) produced by the independent data center. Participants, investigators and physicians taking care of subjects will be blind to the assignment.

2.9 Data Entry and Quality control of data

The data collection will be recorded in the Case Report Forms (CRFs). The CRFs will be filled out truly and accurately and the electronic version of CRF will be accomplished in a Web-based data management system at http://218.17.160.110:8081/login.aspx. In order to keep the data qualities, we will adopt some valid measures to assure information authenticity, accuracy, integrality, seasonable sex.

2.10 statistical analysis

All data will be managed and analyzed by a specialized statistician using the intent-to-treat approach for the evaluation of drug efficacy, the per-protocol analysis for adherence, and safety analysis for adverse events. The efficacy of two treatments (placebo vs. Tanshinone capsules; within-participants effects before vs. after treatment) will compared by ANOVA. The analysis for data statistical evaluation will be performed using the SPSS program, version 16.0 (SPSS Inc., Chicago, IL) and a P value < 0.05 will be considered statistically significant.

3. summary

With the increase in the number of PCOS, more and more patients turn to complementary and alternative medicine for treatment. CHM can regulate and strengthen the hormonal systems of the

wholebody, which is a natural approach for treating PCOS. The significant advantages of CHM may be safe, effective, multi-targets and multiple methods for treating hyperandrogenism in PCOS [13-15].

References:

[1] March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, and Davies MJ,"The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria," Hum Reprod, 2010,25(2):544–551.

[2] Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W et al, "2006 Criteria for defining polycystic ovary syndrome as a predominantly hyperandrogenic syndrome: an androgen excess society guideline," J Clin Endocrinol Metab, 2006, 91(11):4237–4245.

[3] Sartor BM and Dickey RP, "Polycystic ovarian syndrome and the metabolic syndrome," Am J Med Sci, 2005,330(6):336–342.

[4] DeUgarte CM, Bartolucci AA and Azziz R, "Prevalence of insulin resistance in the polycystic ovary syndrome using the homeostasis model assessment," Fertil Steril,2005,83(5):1454–1460.

[5]Escobar-Morreale HF, Luque-Ramirez M and Gonzalez F, "Circulating inflammatory markers in polycystic ovary syndrome: a systematic review and meta analysis, " Fertil Steril, 2011,95(3):1048–1058.

[6]ACOG Committee on Practice Bulletins--Gynecology, "ACOG Practice Bulletin No. 108: Polycystic ovary syndrome, "Obstet Gynecol,2009,114(4):936-949.

[7] Badawy A, Elnashar A, "Treatment options for polycystic ovary syndrome," Int J Womens Health,2011,8(3) :25-35.

[8]Han J-Y, Fan J-Y, Horie Y, Miura S, Cui D-H, et al, " Ameliorating effects of compounds derived from Salvia miltiorrhiza root extract on microcirculatory disturbance and target organ injury by ischemia and reperfusion," Pharmacology & Therapeutics, 2008,117(2): 280–295.

[9] Kang BY, Chung SW, Kim SH, Ryu SY and Kim TS, "Inhibition of interleukin-12 and interferon-gamma production in immune cells by tanshinones from Salvia miltiorrhiza," Immunopharmacology, 2008,49(3):355-361.

[10] Zhang Y, Jiang P, Ye M, Kim SH, Jiang C and Lü J, "Tanshinones: sources, pharmacokineticsand anti-cancer activities," Int J Mol Sci,2012,13(10):13621-1366.

[11] Yang X, Zhang Y, Wu X, Bae CS, Hou L, Kuang H, et al, "Cryptotanshinone reverses reproductive and metabolic disturbances in prenatally androgenized rats via regulation of ovarian signaling mechanisms and androgen synthesis," Am J Physiol Regul Integr Comp Physiol, 2011,300(4):869–875.

[12] Will MA, Palaniappan M, Peegel H, Kayampilly P and Menon KM, "Metformin: direct inhibition of rat ovarian theca-interstitial cell proliferation," Fertil Steril, 2011,98(1):1063-1070.

[13] Jue Zhou and Fan Qu, " Treating gynaecological disorders with traditional chinese medicine: a review," Afr J Tradit Complement Altern Med, 2009,6(4):494–517.

[14] Xihe Li, Xinming Yang, Xiaoke Wu, Lihui Hou and Yan Peng, " Effects of cryptotanshinone in lowering androgens synthesis for the prenatally androgenized male rats," Chinese Journal of Integrated Traditional and Western Medicine, 2008,28(11)1001-1004,.

[15]Junxiu Xing, Yuehui Zhang, Min Hu,Fenghua Xu, Xiaoke Wu and Lihui Hou, " Tanshinone effect on the expression of IRS-1 and p-ERK in trophoblastic cells under insulin resistance," Science & Technology Review, 2009,4(7):75-79.