

Clinical Experience With DLB3233, A Combinations Of Cinnamomum Burmannii And Lagerstroemia Speciosa, For Polycystic Ovar~1

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CLINICAL EXPERIENCE WITH DLBS3233, A COMBINATION OF *CINNAMOMUM BURMANNII* AND *LAGERSTROEMIA SPECIOSA*, FOR POLYCYSTIC OVARY SYNDROME TREATMENT

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ABSTRACT

Objective: DLBS3233, a new insulin sensitizing agent for Type 2 diabetes, is a combination-bioactive-fraction derived from two herbs, i.e., *Lagerstroemia speciosa* and *Cinnamomum burmannii*. Since insulin resistance plays a central pathogenic role in polycystic ovary syndrome (PCOS), DLBS3233 has the potential to benefit women with such a condition, in whom menstrual irregularity, chronic anovulation or infertility are manifested. This clinical study was performed to evaluate the clinical efficacy of DLBS3233 as a single pharmacological therapy in improving follicle maturity in women with PCOS measured by a transvaginal ultrasonography (USG).

Methods: The open study enrolled 14 PCOS subjects from the Obstetrics and Gynecology Department of Sam Ratulangi University/Prof. Dr. Kandou Hospital, satellite hospitals, and private practices. Patients were measured for the dominant follicle diameter using transvaginal USG. Subjects were given DLBS3233 capsule at a dose of 1 capsule at 100 mg once daily for 30 days of the treatment. At the end of the study, patients' follicle diameters were re-assessed. The difference in follicle diameters was compared within the group (within-subject) by paired t-test, with a significance level (α) of 0.05.

Results: Among 14 PCOS enrolled subjects, 57.2% aged between 26 and 30 years old. There were similar proportions of subjects with normal body mass index (42.8%) and overweight (42.8%). Before treatment (at baseline), the mean follicle diameter was 4.094 ± 1.016 mm. After 30 days of treatment, it increased significantly to 8.594 ± 1.647 mm ($p < 0.001$ versus baseline). There were 10 subjects (71.4%) showed follicles with size ranging between 5 and 10 mm, while the remaining 4 subjects (28.6%) had them bigger than 10 mm.

Conclusion: Through this study, DLBS3233 at the dose of 100 mg once daily for 30 days showed a potential benefit for PCOS patients, particularly in improving follicle maturity expressed as an increased follicular diameter.

Keywords: DLBS3233, *Cinnamomum burmannii*, Follicle diameter, *Lagerstroemia speciosa*, Polycystic ovary syndrome.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is the most common endocrine disorder in women. It affects 5-10% women of reproductive age and contributes up to 15-20% to anovulation among infertile women [1]. Peripheral insulin resistance involving both intrinsic and acquired defects in insulin signaling likely plays a central pathogenic role in PCOS. Cellular insulin resistance in PCOS has been further implied to involve a novel post-receptor defect in insulin signal transduction [1,2]. Hyperinsulinemia may have gonadotropin-augmenting effects on ovarian function [1]. In addition, insulin resistance in PCOS has been associated with lowered adiponectin level, a hormone secreted by adipocytes that regulate lipid metabolism and glucose levels. Both lean and obese women with PCOS have lower adiponectin levels than women without PCOS [1]. Thus, insulin resistance contributes to increased risk for pregnancy complications, diabetes, and cardiovascular disease risk profile in PCOS, which is further exacerbated by obesity [2].

Insulin resistance is also thought to play a central role in the development of the metabolic syndrome [3,4]. The prevalence of the metabolic syndrome is much higher in women with PCOS (33-46%) [5-7] compared with normal women (6% of women aged 20-29 years and 15% of those aged 30-39 years) [8]. The metabolic syndrome has been associated with an increased risk of incident diabetes, cardiovascular disease, and cardiovascular mortality [9-11]. Consequently, women with PCOS are at increased risk for Type 2 diabetes, dyslipidemia, hypertension, and atherosclerosis [12-15].

The mainstream of PCOS therapy, ovulation induction with clomiphene citrate, has been shown to have a high rate of failure since such therapy

alone does not interfere with insulin resistance which is, in fact, of high prevalence (64.4%) among PCOS women [16]. Therefore, treatment of PCOS has currently been involving therapy to improve the insulin resistance through lifestyle therapy or with a diabetes drug.

The treatment of PCOS with pioglitazone, like other thiazolidinediones, may result in ovulation in some premenopausal anovulatory women [17,18]. Compared with placebo, pioglitazone treatment in PCOS was associated with improvements in insulin action and glucose homeostasis and ameliorated the hyperandrogenic ovarian response [19]. However, pioglitazone treatment have been associated with exacerbate or lead to congestive heart failure [20,21], edema [22,23], weight gain [24], anemia [25], liver toxicity [26-28], lowered bone density, and increased fracture risk [29,30].

DLBS3233 is a new insulin sensitizing agent for Type 2 diabetes. DLBS3233 is a combination-bioactive-fraction derived from two herbs, i.e., *Lagerstroemia speciosa* and *Cinnamomum burmannii*. Preclinical studies of DLBS3233 have shown that it increased the expression of phosphatidylinositol-3-kinase, Akt, glucose transporter (GLUT-4), peroxisome proliferator-activated receptor gamma (PPAR- γ) and PPAR- δ at the mRNA level of 3T3 Swiss Albino preadipocyte cells. It also reduced the expression of resistin gene and increased the expression of GLUT-4 and adiponectin at mRNA level [31,32]. DLBS3233 administered to insulin resistant Wistar rats showed an ability to control blood sugar, insulin levels, and other lipoproteins, including high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol [32]. Acute toxicity [33], subchronic toxicity [34], and teratogenic [35] studies have proven the safety of DLBS3233.

Based on pharmacological activities of DLBS3233, it was hypothesized that the agent may pose benefits to PCOS-laden female patients. This study was aimed at clinical evaluation of DLBS3233 in improving follicle maturity in women with PCOS measured by transvaginal ultrasonography (USG).

METHODS

Female patients with PCOS, who came to the Obstetrics and Gynecology Department of Sam Ratulangi University/Prof. Dr. Kandou Hospital, satellite hospitals, and private practices, since July 2014 to November 2014, were recruited for this study. The inclusion criteria were female patients at reproductive age (i.e., 18-40 years old) and the diagnosis of PCOS confirmed by fulfilling, at least, two of the Rotterdam criteria [36]. Patients were excluded if they were pregnant or lactating; known to have any of the following conditions which may also cause hyperandrogenism, such as Cushing's syndrome, late onset of congenital adrenal hyperplasia, androgen secreting tumors, uncontrolled thyroid disease, and hyperprolactinemia. Patients with the current medical condition as judged by the investigator could jeopardize subject's health or interfere with the study evaluation, such as Diabetes mellitus, other cardiovascular diseases (symptomatic ischemic heart disease, unstable angina pectoris, heart failure), and medically-assisted weight loss with medications or surgical procedures were also excluded.

The study protocol had been reviewed and approved by the Ethics Committee of Prof. Dr. Kandou Hospital, prior to the study conduct. Written informed consent was obtained from each subject prior to their participation.

This was an open study with DLBS3233 involving PCOS subjects. Study subjects were measured for the follicle diameter using transvaginal USG. Subjects were given DLBS3233 capsule 100 mg once daily after breakfast, over 30 days of the treatment. At the end of the study, patients were re-assessed for follicle diameter. The follicle diameter was compared within groups by paired t-test ($\alpha=0.05$). A statistical analysis was done using SPSS version 20.0. All continuous variables are presented as mean \pm standard deviation, while categorical variables are presented as number (proportion in %).

RESULTS

There were 14 eligible subjects recruited for this study, with all subjects showed PCOS as confirmed by two of the Rotterdam Criteria 2003 [36]. The most subjects (57.2%) aged between 26 and 30 years old. There were similar proportion of subjects having normoweight (42.8%) and overweight (42.8%). Baseline characteristics are shown in Table 1.

The most subjects (71.4%) had follicles with size ranging between 2 and 4 mm before administration of DLBS3233. After 30 days of treatment with DLBS3233, there were 10 subjects (71.4%) showed follicle sizes ranging between 5 and 10 mm on USG examination; and 4 subjects (28.6%) with follicle sizes bigger than 10 mm. The proportions of subjects with certain follicle size are presented in Table 2. The mean diameters of the follicle before and after treatment of DLBS3233 are shown in Table 3.

DISCUSSION

The efficacy of DLBS3233 in this study was measured as the improvement of follicle size, which confers the state of follicular maturity in women with PCOS. The follicle size was measured using transvaginal USG.

In the United States (US), some studies report that the prevalence of overweight and obesity in women with PCOS is as high as 80%. Outside the US, the prevalence of obesity in affected women is lower, although it increased overtime with studies reported rates as low as 20% [37]. Many women with PCOS are overweight, although about one-third to one-half of women with PCOS actually is of normal weight [38].

Table 1: Baseline characteristics of study subject

Characteristic	N (%)
Age	
18-25 years old	-
26-30 years old	8 (57.2)
31-35 years old	2 (14.3)
36-40 years old	4 (28.5)
BMI (kg/m ²)	
18.0-24.9 (normoweight)	6 (42.8)
25.0-29.9 (overweight)	6 (42.8)
≥30.0 (obese)	2 (14.4)

N: Number of subjects, BMI: Body mass index

Table 2: Proportion of subjects with certain follicle size (expressed in diameter) before and after treatment of DLBS3233

Follicle diameter (mm)	Before N (%)	After N (%)
<2	-	-
2-4	10 (71.4)	-
5-10	4 (28.6)	10 (71.4)
>10	-	4 (28.6)
Total	14 (100)	14 (100)

N: Number of subjects

This was also reflected in our study, 42.8% subjects with PCOS had normoweight, while 42.8% and 14.4% subjects were overweight and obese, respectively (Table 1). PCOS is associated with defects in insulin sensitivity and secretion that are further exacerbated by obesity. Obese women are more likely to have menstrual irregularity and anovulatory infertility than normal-weight women. In reproductive-age women, the relative risk of anovulatory infertility increases at a body mass index (BMI) of 24 kg/m² and continues to rise with increasing BMI [37].

According to a study by Brettenthaler *et al.* [39], pioglitazone given for 3 months in patients with PCOS significantly increased the rate of induction of ovulation from 5.6% to 41.2% compared with a placebo control group. Our study with DLBS3233, a natural-origin insulin sensitizer, showed that proportion of subjects with follicle diameter 5-10 mm increased from 28.6% at baseline to 71.4% after 30 days of treatment. Further, there were 28.6% of subjects showing follicle diameter >10 mm at the end of treatment (Table 2). Even though a follicle is regarded mature and counts as ovulation if its diameter is ≥ 16 mm [40], the significantly increasing size of the follicles after treatment (Table 3) may be seen as an early indication of a clinical improvement in fertility. This promising result was likely due to an indirect impact of the improvement in insulin resistance by DLBS3233. DLBS3233 exerts its action through phosphorylation at tyrosine residue of the insulin receptor substrate. Furthermore, the mechanism of action for DLBS3233 is involving the stimulation of PPAR- γ , thereby increasing insulin sensitivity and reducing insulin resistance [32]. The improvement of insulin resistance contributes to the development of ovarian follicle becoming mature follicle.

DLBS3233 was very well tolerated by all study subjects. There were no adverse events occurred during this study.

Altogether, these results showed that DLBS3233 could possibly be considered an option therapy for women with PCOS.

The limitations of this study were the small sample size, open study and short duration of treatment. Besides, we did not select the PCOS subjects limitedly to those with insulin resistance, a population who is likely to benefit more from DLBS3233 treatment. Despite those limitations, however, the results of this study have provided a preliminary evidence of the efficacy of DLBS3233 treatment in improving follicle diameter

Table 3: Follicle size before and after treatment of DLBS3233

Timepoint evaluation	Follicle diameter (mm) Mean±SD	Minimum (mm)	Maximum (mm)	95% confidence interval	p*
Before	4.094±1.016	2.5	6.1	(-) 0.9704-(-) 0.7607	<0.001
After	8.594±1.647	6	11.7		

SD: Standard deviation

in patients with PCOS. Indeed, based on such promising findings we are currently conducting larger randomized clinical studies with a longer study period as well.

CONCLUSION

Through this study, DLBS3233 at the dose of 100 mg once daily for 30 days showed a potential benefit for PCOS patients, particularly in improving follicle maturity expressed as an increased follicular diameter.

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