Randomized Controlled Trial

A lecithin phosphatidylserine and phosphatidic acid complex (PAS) reduces symptoms of the premenstrual syndrome (PMS): Results of a randomized, placebo-controlled, double-blind clinical trial

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S U M M A R Y

Background & aims: Many women experience emotional and physical symptoms around the time of ovulation and more so before menstruation interfering with their daily normal life also known as premenstrual syndrome (PMS). Recent observational data suggest that supplementation with Lipogen’s phosphatidylserine (PS) and phosphatidic acid (PA) complex (PAS) alleviates these PMS symptoms. The aim of this study was to confirm these observations on the effects of PAS on PMS symptom severity within a controlled clinical trial setting.

Methods: Forty women aged 18–45 years with a diagnosis of PMS were assigned to either take PAS (containing 400 mg PS & 400 mg PA per day) or a matching placebo. The study comprised 5 on-site visits including 1 baseline menstrual cycle followed by 3 treatment cycles. Treatment intake was controlled for by using an electronic device, the Medication Event Monitoring System (MEMS®). Primary outcome of the study was the PMS symptoms severity as assessed by using the Daily Record of Severity of Problems (DRSP). Further, SIPS questionnaire (a German version of the Premenstrual Symptoms Screening Tool (PSST)), salivary hormone levels (cortisol awakening response (CAR) and evening cortisol levels) as well as serum levels (cortisol, estradiol, progesterone and corticosteroid binding globulin (CBG)) were assessed.

Results: PMS symptoms as assessed by the DRSP Total score showed a significantly better improvement (p = 0.001) over a 3 cycles PAS intake as compared to placebo. In addition, PAS treated women reported a greater improvement in physical (p = 0.002) and depressive symptoms (p = 0.068). They also reported a lower reduction of productivity (p = 0.052) and a stronger decrease in interference with relationships with others (p = 0.099) compared to the placebo group. No other DRSP scale or item showed significant results. Likewise, the reduction in the number of subjects fulfilling PMS or premenstrual dysphoric disorder (PMDD) criteria as classified by the SIPS did not differ between the PAS and the placebo group. For the biomarkers, the salivary cortisol percentage increase of the CAR was significantly less pronounced (p = 0.068). They also reported a significantly better improvement in the follicular phase of cycle 4 than in the follicular phase of cycle 1 for subjects taking PAS when compared to subjects taking placebo (p = 0.018). Furthermore, the change of serum cortisol levels between visit 1 and visit 5 differed significantly between groups (p = 0.043). While serum cortisol levels of PAS treated females slightly decreased between visit 1 and visit 5, cortisol levels of females treated with placebo increased. For all other biomarkers, no treatment effects were observed over the 4 cycles study period.

Abbreviations: AE, adverse event; AUC g, area under the curve (ground); AUC i, area under the curve (increase); BMI, body mass index; CAR, cortisol awakening response; CBG, corticosteroid binding globulin; CI, confidence interval; CLIA, chemiluminescence immunoassay; CRD, clinical research organization; DRSP, Daily Record of Severity of Problems; DSM, Diagnostic and Statistical Manual of Mental Disorders; HR, heart rate; ITT, intention to treat; MEMS, Medication Event Monitoring System; Mini-DIPS, Diagnostisches Kurz-Interview bei psychischen Störungen; PA, phosphatidic acid; PAS, phosphatidylserine/phosphatidic acid complex; PMDD, premenstrual dysphoric disorder; PMS, premenstrual syndrome; PP, per-protocol; PS, phosphatidylserine; PSST, Premenstrual Symptoms Screening Tool; SIPS, Screening-Instrument fuer Praemennstruelt Symptome; TSH, thyroid stimulating hormone; V, visit; WOM, word of mouth.

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1. Introduction

PMS is characterized by a cluster of somatic and psychological symptoms of varying severity. These symptoms occur only during the luteal phase of the menstrual cycle and resolve during the first days of menses [12].

The estimated prevalence of PMS varies. A systematic review reports a pooled PMS prevalence of 47.8%. This indicates that about half of women within their reproductive age experience PMS symptoms. This typically can include feeling tired, irritability, mood changes, bloating, skin irritations and breast tenderness. In addition, an increasing trend in the prevalence of PMS during 1996–2001 has been observed [8].

The etiology of premenstrual disorders is multifactorial. Precise causes and the influence of heritability are still unknown and not sufficiently explored yet [10]. The DSM-5 [2] states that the onset of PMDD, a more severe form of PMS with a prevalence of 3–8% [16,37], can occur at any point after menarche; symptoms cease after menopause but can be triggered by cyclical hormone replacement. Stress is also a factor in PMS and PMDD along with a history of interpersonal trauma and seasonal changes. Premenstrual symptoms can be improved by pharmacological interventions (e.g. oral contraceptives, antidepressants) or by nutrition.

An association between nutritional factors and PMS has been observed repeatedly (Cheng et al., 2013 [40]; Bertone-Johnson et al., 2014 [39]; Kia et al., 2015 [43]; Chocano-Bedoya et al., 2013 [41]; Gorczyca et al., 2016 [42]) and consequently the search for a nutritional supplement that is effective in alleviating PMS symptoms is of great interest. To many, this seems to be a more attractive alternative when compared to intake of pharmaceutical and psychiatric drugs.

PAs are the acid forms of phosphatidates, which are a part of common phospholipids. PA has different roles in the cell: It is a precursor for other lipids such as PS or phosphatidylcholine via the conversion of PA to diacylglycerol [3]. Moreover, PA influences membrane curvature [22,25] and acts as a signaling lipid [11,34]. In combination with PS, PA has shown to lower cortisol levels and dampens mood and stress management [4,17]. PS, a phospholipid component is found in mammalian cell membranes. Previous studies indicated that acute and long-term administration of PS dampens cortisol responses to acute exercise and mental stress [17,26,36]. In addition, PS has shown to improve memory, learning, mood and stress management [4,17–20,38]. Further, the intake of PS has been associated with an improvement of psychiatric disorders, such as bipolar and major depressive disorders (reviewed in Refs. [12,20]) and with the prevention of inflammatory neurodegenerative events [29].

Between December 2011 and March 2012, Lipogen Ltd. performed a word of mouth (WOM) marketing campaign in the United States of America (WOM company BzzAgent, USA). 23 out of 220 women (10.45%), age <40, who consumed the product for 2 months, reported improvement in PMS. The following study was performed to confirm this effect in a single center, double-blind, placebo-controlled, randomized clinical trial.

2. Materials and methods

2.1. Study participants

Eligible participants were women aged 18–45 years with a PMS diagnosed by a gynecologist. Participants were required to have regular menstrual cycles with constant cycle duration (25–35 days) and easy access to computer and internet at home.

Participants were not eligible if any of the following exclusion criteria applied: Known allergies to ingredients of the test substance; any underlying psychiatric disorder (e.g. major depressive disorder) as assessed with the Mini-DIPS (Diagnostisches Kurz-Interview bei psychischen Störungen; [24]); any current/acute illness; any disease other than minor medical conditions (e.g. seasonal allergies); current intake of any drugs besides thyroid medication (TSH (thyroid stimulating hormone) values in the normal range according to lab results within the past 12 months) and blood pressure medication (stable for 6 months); intake of nutritional supplements or homeopathic remedies within the 2 weeks prior to the first visit; strict diet or excessive sport activities; smoking more than 5 cigarettes per week; working night shifts; pregnant or lactating; planning to get pregnant during the next 12 months; employee of the Sponsor or CRO (clinical research organization); investigator doubts truthfulness of self-reported health information; women otherwise apparently unsuited (lack of cognitive or verbal skills); or currently participating in another clinical study.

The study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonization/Good Clinical Practice (2008). The protocol received approval from the Ethics Commission of the State Chamber of Medicine in Rhineländ-Palatinate (Deutschausplatz 3, 55116 Mainz, Germany). Written informed consent was obtained from each participant before study enrollment.

2.2. Study design

This prospective, randomized, double-blind, placebo-controlled, single center study with 2 treatment arms (PAS or placebo) was conducted in Trier, Germany between July 2015 and July 2016. Each woman completed detailed assessments over a period of 4 menstrual cycles. The objective was to evaluate the effects of 3 cycles intake of PAS on PMS following a first baseline observational cycle.

The study included 5 visits. Forty eligible women were randomly assigned to either the PAS or placebo group. EightOverall, this study confirms that a daily intake of PAS, containing 400 mg PS and 400 mg PA, can be considered as safe.

Conclusions: Results substantiate the efficacy of PAS in reducing symptoms of PMS. In view of the recent inclusion of severe PMS symptoms (PMDD) in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), the positive results of this clinical study merits consideration of developing the PAS complex as a botanical drug for treatment of PMDD.

Clinical trial registration: The study is registered at Deutsches Register Klinischer Studien with the registration number DRKS00009005. © 2018 The Authors. Published by Elsevier Ltd on behalf of European Society for Clinical Nutrition and Metabolism. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
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