

THE EFFICACY OF ORAL ADMINISTRATION OF RESVERATROL IN ASSOCIATION WITH FEVERFEW (REVIFASTDOL[®]) FOR THE TREATMENT OF PRIMARY DYSMENORRHEA: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Objective: To evaluate the efficacy of oral administration of resveratrol in association with feverfew (RevifastDol[®], S&R Farmaceutici S.p.A., Italy) in the treatment of primary dysmenorrhea.

Methods: This study was based on a retrospective analysis of a prospectively collected database including 30 women of reproductive age suffering primary dysmenorrhea. Patients received RevifastDol[®] (two tablets per day for 6 months) starting three days before the beginning of the menstrual cycle and each day during the menstrual period. The intensity of dysmenorrhea was assessed by using a 10-cm visual analogue scale. The short-form health survey (SF-36) was used to investigate the quality of life.

Results: At 6-month follow up, 73.3% of the patients were either satisfied or very satisfied with the treatment. Since the first month and during all the study period, there was a significant amelioration in the intensity of dysmenorrhea compared with baseline ($p < 0.05$). At 6-month follow-up there was a significant reduction in the number of analgesic pills taken each day during the menstrual period and quality of life significantly improved.

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Conclusion: The oral administration of resveratrol in association with feverfew significantly decreased the intensity of primary dysmenorrhea and the need for analgesics pills in these patients; furthermore, it improved the quality of life of the study participants.

Keywords: Feverfew; Primary dysmenorrhea; Quality of life; Resveratrol; Therapy

Introduction

Primary dysmenorrhea is the most common gynecological disorder in women of reproductive age [1, 2]. It is defined as painful menstrual cramps of uterine origin in the absence of pelvic pathologies [3]. The cramping sensation in the lower abdomen is often accompanied by other systemic symptoms, such as sweating, headaches, nausea, vomiting, diarrhea, and tremulousness, all occurring just before or during the menses [3]. Almost half of these women experience dysmenorrhea, and in 15% of them, the pain has an impact on daily activities, work, and academic performance. Primary dysmenorrhea is associated with an abnormal secretion of prostaglandins (PGs) during menstruation; the enhanced release of PGs is believed to cause myometrial hypercontractility, resulting in ischemia and hypoxia of the uterine muscle, and, ultimately, pain [4, 5].

Pain control is the main goal of treatment. Usually, primary dysmenorrhea is treated with nonsteroidal anti-inflammatory drugs (NSAIDs) such as mefenamic acid and ibuprofen [6, 7]; however, these treatments may cause gastrointestinal side effects [8, 9]. Herbal medicines and homeopathy are an alternative which have been used for many years [10]. Scientific studies support the use of herbal medicines as a viable option for the treatment of primary dysmenorrhea [11-15]. Resveratrol (trans-3,5,40-trihydroxystilbene) is a natural phytoestrogen synthesized by plants following ultraviolet radiation. Red wine, peanuts, grapes, and berries have significant concentrations of this compound. Resveratrol has been reported to have anti-inflammatory [16] and antioxidant properties [17]. Recent studies documented that resveratrol has various health benefits, such as cardiovascular and cancer preventive properties. One of the possible mechanisms for its protective activities is the downregulation of the inflammatory responses. *Tanacetum parthenium* L. belongs to the Asteraceae family and it is a perennial herb commonly known as Feverfew. *T. parthenium* contains many sesquiterpene lactones, with high concentration of parthenolide (up to 85% of the total sesquiterpene content), lipophilic and polar flavonoids in the leaves and the flower heads [18]. Feverfew is a medicinal plant traditionally used for the treatment of fevers, migraine headaches, rheumatoid arthritis, stomach aches, toothaches, insect bites, infertility, and problems with menstruation, and labor during childbirth [19]. It has been proved that the biological activity of the plants results from the presence of the chemical compounds with different structures, including the sesquiterpene lactones, which include parthenolid, determining the anti-migraine properties of the plants [20]. A proposed mechanism of action involves parthenolide specifically binding to and inhibiting I κ B kinase complex (IKK) β . IKK β plays an important role in pro-inflammatory cytokine-mediated signaling. Research up to date on preclinical and clinical nature demonstrates the efficacy of plants in the prevention of migraine attacks [21]. Feverfew is safe and recorded side effects are mild and transient. Although, the well documented usage for migraine headaches [21-23], historically feverfew was used also to manage with premenstrual pain and disorders.

The primary aim of this study is to evaluate the efficacy of the oral administration of resveratrol in association with feverfew (RevifastDol[®] S&R Farmaceutici S.p.A. Bastia Umbra, PG, Italy) for treating primary dysmenorrhea. The secondary objective is to assess patients' satisfaction.

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Materials and Methods

Study participant

This was a retrospective analysis of a prospectively collected database including women of reproductive age suffering primary dysmenorrhea. Patients attended our clinic between September 2016 and January 2017. Inclusion criteria for the treatment with RevifastDol® were age between 18 and 45 years, regular menstrual cycles, diagnosis moderate or severe primary dysmenorrhea (pain score of least 4 on a 10-cm visual analogue scale [VAS]) persisting for at least 6 months at the time of consultation. The exclusion criteria were a history of allergy to ingredients contained in RevifastDol®, use of intrauterine devices, use of oral contraceptive pills or corticosteroids, breastfeeding, and other medical history which can cause abdominal pain (such as gall bladder, gallstone, dyspepsia, or irritable bowel syndrome). Primary dysmenorrhea was confirmed by the exclusion of other pelvic pathologies by ultrasonography (such as endometriosis, adenomyosis and hydrosalpinx). All patients underwent transvaginal ultrasonography by using a Voluson E6 or Voluson S8 machine (GE Healthcare, Milwaukee, WI, USA), and those who met the inclusion criteria were offered the treatment with RevifastDol®. Patients accepting to use RevifastDol® signed a written consent form to collect data for clinical audit and scientific purposes. Women were informed that there is no evidence on the effects of RevifastDol® in treating primary dysmenorrhea.

Outcomes of the study

The primary outcome of the study was to assess the impact of RevifastDol® on dysmenorrhea intensity. The secondary outcomes were the assessment of quality of life and the evaluation of the number of analgesic pills used during the study period.

Patients received the following treatment: RevifastDol® (Parthenium dry extract 400 mg of which Parthenolide 2 mg, and Revifast® 320 mg of which Resveratrol 96 mg) two tablets per day. Patients were instructed to take two tablets starting three days before the beginning of the menstrual cycle and each day during the menstrual period for 6 months. The patients had to record the average pain score at the end of each menstrual period. Patients were allowed to take NSAIDs when needed (ibuprofen 600 mg); however, they were asked to record the number of tablets used each month during treatment.

Assessment of symptoms

An electronic database (Gineko, COSA Srl, Rome, Italy) was used to record the demographic and clinical characteristics of the patients. Patients recorded in a diary the intensity of dysmenorrhea during each menstrual cycle throughout a 10-cm visual analogue scale (VAS); the left extreme of the scale indicating the absence of pain and the right indicating the worst pain possible. Furthermore, they recorded the number of ibuprofen tablets taken each menstrual cycle. An intention-to-treat analysis was performed at 6 months to evaluate the overall degree of satisfaction with the treatment. The women rated the overall degree of satisfaction with their treatment by answering the following question: 'Taking into consideration the variations in pain symptoms, in overall well-being and quality of life, as well as the adverse effects experienced, if any, how would you define the level of satisfaction with your treatment?' as previously described [24]. Answers were based on a 5-point Likert scale (very satisfied, satisfied, uncertain, dissatisfied, very dissatisfied). The short-form health survey (SF-36) was administered to the patients at baseline and after 6 months of therapy and was used to investigate the quality of life. The SF-36 is one of the most common tool available in this field and the reliability and

validity of its Italian version has been confirmed. The questionnaire includes 36 items, 8 scales, and 2 (physical and mental health) components, with a score ranging from 0 to 100, where 100 indicate the highest situation [25].

Sample size and statistical analysis

Considering a mean value of 6.0 and a standard deviation (SD) of 2.3 for menstrual pain intensity based on the results of a study carried out in the same setting [26], $\alpha=0.05$, $\beta = 0.20$, and 10% possible drop out, the sample size was calculated to be 27 patients to detect at least 20% reduction in the mean of pain intensity due to the intervention ($m_2 = 4.8$ with $sd_2 = 2.3$ [same as the baseline] for SD). This sample size is enough to detect at least 10% improvement in the mean components of quality of life due to the intervention with a power of 90%.

Categorical variables were compared by using the chi-squared test and the Fisher exact test. Changes in severity of symptoms during treatment in the study group were analyzed by using the paired t-test and the signed rank test according to data distribution. Data were analyzed using the SPSS software version 20.0 (SPSS Science, Chicago, IL, USA).

Results

A total of 30 patients with primary dysmenorrhea were included in the study (Figure 1).

Figure 1: Flow chart of the study

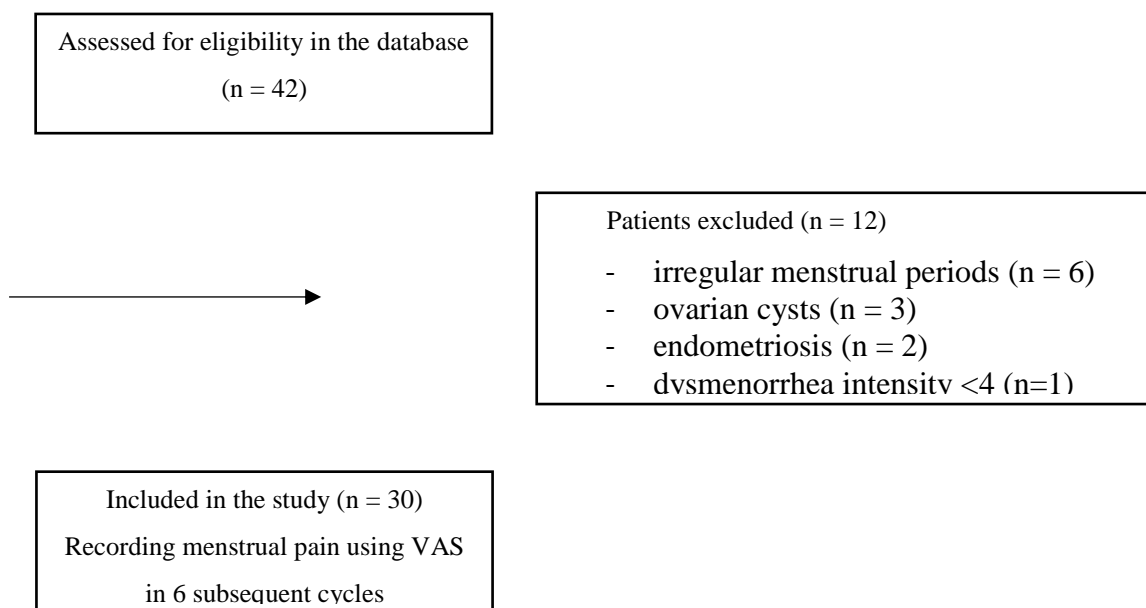


Table 1 shows the characteristics of the women enrolled in the study. The average age of the participants was 27.5 ± 5.3 years. Only 13.3% of the women were in the age group of 20 years and below; while the majority of the women (70%) were between the ages of 20 and 30 years. The mean BMI of the patients was $22.5 (20.0-24.75)$ kg/m^2 and the prevalence of overweight (defined as $\text{BMI} > 25 \text{ kg}/\text{m}^2$) was 16.7% ($n = 5$). The patients' average menarche age was 11.25 ± 1.27 , ranging from 11 to 13; most patients' menarche age was between 12 and 15 (70%). The average menstrual bleeding duration was 6.0 ± 1.51 days. Most patients' menstrual bleeding duration was less than 7 days (60.0%) (Table 1).

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Table 1. Demographic and clinical characteristics of the patients included in the study

	Patients (n=30)
Age (years, mean \pm SD)	27.5 \pm 5.3
Nulliparous n (%)	27 (90)
Race (n, %)	
Caucasian	26 (86.6)
Afro-Caribbean	3 (10.0)
Asian	1 (3.4)
Others	0 (0.0)
BMI (median, IQR)	22.5 (20.0-24.75)
Menarche (Median, IQR)	12 (11.25-13)
Length of menstrual cycle (days, mean \pm SD)	6 \pm 1.50

SD: standard deviation; BMI: Body Mass Index; IQR: interquartile range

At 6-month follow up, the intention-to-treat analysis including all the 30 patients showed that 33.3% of women were very satisfied, 40% were satisfied, 20% were uncertain and 6.7% were dissatisfied.

Table 2. Comparison of the intensity of dysmenorrhea during the study period

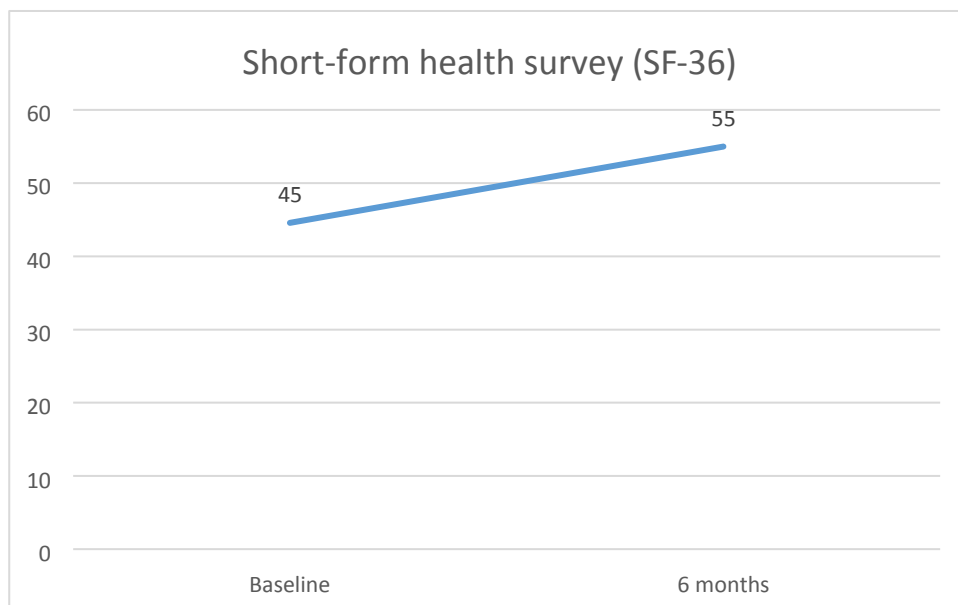
Symptom	Baseline	1 month	2 months	3 months	4 months	5 months	6 months
Dysmenorrhea (mean, \pm SD)	6.29 \pm 0.80	5.91 \pm 0.71	5.52 \pm 0.72	5.17 \pm 0.80	4.82 \pm 0.74	4.38 \pm 0.71	4.07 \pm 0.64
P value*		p<0.05	<0.05	<0.05	<0.05	<0.05	<0.05

SD: standard deviation;

*Intensity of symptoms compared with baseline

Table 2 shows the changes in dysmenorrhea scores during treatment. Since the first month and during all the study period, there was a significant amelioration in the intensity of dysmenorrhea compared with baseline ($p < 0.05$). Moreover, at 6-months there was a significant reduction in the number of analgesic pills (median, IQR) taken each day during the menstrual period [baseline: 2 (1-3) versus 6 months: 0.5 (0-1); $p < 0.05$].

Figure 2. Short-form health survey (SF-36) scores during the study period



Values are mean ± standard deviation (SD) shown by vertical bars. EHP subdomains scores range from 0 to 100. Higher score indicates fewer negative symptoms

The overall SF-36 score variation during the study period is shown in Figure 2. There was a significant amelioration in several SF-36 domains after 6 months of treatment with Revifastdol®. The average scores obtained from the SF-36 scale for each domain at 6 months are presented in Table 3.

Table 3. Average scores obtained from the SF-36 scale for each domain at 6 months

Domains	SF-36 score baseline (mean; ± SD)	SF-36 score 6 months (mean; ± SD)	P value
Physical functioning	43.23 ± 9.86	66.20 ± 13.31	<0.05
Role-physical	51.76 ± 8.09	53.70 ± 7.46	0.799
Bodily pain	50.73 ± 8.27	54.76 ± 7.45	0.548
General health perception	44.40 ± 9.18	67.30 ± 11.27	<0.05
Vitality	36.10 ± 6.95	38.66 ± 7.18	0.655
Social functioning	41.80 ± 8.84	66.20 ± 13.31	<0.05
Role-emotional	38.90 ± 8.12	41.20 ± 9.02	0.879
Mental health	49.65 ± 8.75	51.87 ± 8.14	0.745

SD: standard deviation; SF-36: short-form health survey

Discussion

The present study shows that a nutraceutical combination of resveratrol and feverfew (Revifastdol[®]) significantly decrease the intensity of primary dysmenorrhea and the need for analgesics pills in these patients; furthermore, it was able to significantly improve the quality of life of the study participants. After 6 months of treatment with Revifastdol[®] 33.3% of women were very satisfied and 40% were satisfied. The high degree of satisfaction could be due to a significant amelioration in the intensity of dysmenorrhea. Moreover, the changes in in dysmenorrhea scores during treatment is reflected by the reduction of the number of analgesic pills taken each day during the menstrual period.

Because of the PGs -based pathogenesis of primary dysmenorrhea, NSAIDs are the most common pharmacological treatment. The various formulations of NSAIDs have similar efficacy in improving dysmenorrhea; improvement in pain is observed in 64-100% of women [27-29]. Oral contraceptives are usually administered to women who either do not respond or are intolerant to NSAIDs [3]. Oral contraceptives suppress ovulation, reduce the thickness of the endometrium thus reducing the volume of menstrual flow, PGs synthesis and pain [30].

Many women also resort to alternative non-pharmacologic therapies to manage their menstrual discomfort. A recent Cochrane review investigated the role to dietary supplements for the treatment of dysmenorrhea [31]. Interventions included 12 different herbal medicines and five non-herbal supplements (fish oil, melatonin, vitamins B1 and E, and zinc sulphate) in a variety of formulations and doses. The authors judged all the evidence to be of low or very low quality; however, for several supplements there was some low quality evidence of effectiveness and, thus, the authors suggested that more research is justified [30].

To the best of our knowledge, this is the first study that examines the efficacy of oral administration of resveratrol in association with feverfew on pain intensity and quality of life in women with primary dysmenorrhea. Our findings suggest that RevifastDol[®] started before the beginning of the menstrual period is effective in ameliorating the intensity of the menstrual pain since the first months of assumption, and the effect lasts and improves over time. Moreover, the rate of satisfied patients (very satisfied and satisfied) at the end of the 6-month treatment was 73.3%. These results are in line with what published on the effect of homeopathy on pain intensity and quality of life in women with primary dysmenorrhea [26, 31]. A large multicenter observational study including 128 women with primary dysmenorrhea treated with homeopathy showed substantial improvements in the quality of life, although the disease was long-standing, chronic, and conventionally treated [31]. Other clinical trials conducted on patients with other conditions indicate a significant positive effect of homeopathy on pain relief in patients with fibromyalgia [32] and on quality of life improvement in women with premenstrual syndrome [33].

The current study has several limitations. The most relevant limitation of this study is the retrospective analysis of the collected data, a single study group, and the small sample size, which can limit the detection of smaller probable effect size. Moreover, as general observation, especially for industrialized countries, patients using non-conventional therapies tend to be younger and better educated than conventional patients and of higher socioeconomic status. These factors could be indicative for a health-awareness above average and an inclination to additional self-treatment and obtaining higher results.

Considering the limitations of the current study and the absence of previous studies assessing the effect of RevifastDol[®] on primary dysmenorrhea, more trials with a rigorous design, with larger sample size, and randomization are needed to draw definite conclusions on this topic.

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Conclusion

This study indicates a significant effect of RevifastDol® in decreasing pain intensity and in improving quality of life in patients with primary dysmenorrhea.

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