The Effectiveness of *Phalleria macrocarpa Bioactive Fraction in Alleviating Endometriosis and/or Adenomyosis Related Pain*

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Abstract

The overexpression of estrogen receptor-beta (ER-β) and the cyclooxygenase-2 (COX-2) enzyme coupled with the absence of expression of progesterone receptors (PR) is critical to the pathogenesis of endometriosis and adenomyosis associated pain. DLBS1442, a novel bioactive extract of Phaleria macrocarpa, exerts its action by downregulating the overexpressed ER-β and COX-2 products and up-regulating PR gene expression. This pilot study was conducted to evaluate the effectiveness of DLBS1442 treatment in alleviating endometriosis- and/or adenomyosis-related pain. Ten endometriosis and/or adenomyosis patients were recruited consecutively at Yasmin Clinic Dr. Cipto Mangunkusumo General Hospital in January - March 2013. Pain associated with menses, including pre-menstrual pain, dysmenorrhea, dyschezia and dysuria, was measured using the visual analog scale (VAS) at each of the next three menstrual cycles. Patients reporting one or more pain symptoms with a VAS score ≥ 4 were given 100 mg of DLBS1442 three times daily for 12 weeks. VAS score reduction was noted in the first post-treatment menstrual cycle (approximately 5.3 weeks after treatment initiation) and VAS scores continued to decline over the final two cycles. DLBS1442 was effective in alleviating endometriosis- and/ or adenomyosis-related pain, as demonstrated by early pain reduction as evaluated using the VAS.

Keywords: DLBS1442, dysmenorrhea, endometriosis, adenomyosis

Efektivitas Ekstrak Bioaktif *Phaleria macrocarpa* pada Masalah Nyeri Terkait Endometriosis dan/ atau Adenomiosis

Abstrak

Over-ekspresi reseptor estrogen beta (ER-β) dan enzim siklo-oksigenase-2 (COX-2) akan menekan ekspresi reseptor progesteron (PR) di endometrium; hal tersebut penting dalam patogenesis endometriosis dan adenomiosis. DLBS 1442, ekstrak bioaktif Phaleria macrocarpa, bekerja dengan menekan over-ekspresi ER-β dan COX-2 serta meningkatkan regulasi ekspresi gen PR. Studi awal dilakukan untuk mengevaluasi efektivitas pengobatan DLBS1442 pada masalah nyeri terkait endometriosis dan/ atau adenomiosis. Sepuluh penderita endometriosis dan/ atau adenomiosis di klinik Yasmin RSCM pada bulan Januari - Maret 2013 yang memiliki keluhan nyeri diikutsertakan dalam penelitian ini. Dilakukan penilaian skor visual analog scale (VAS) untuk keluhan nyeri pre-menstruasi, dismenorea, diskezia dan disuria setiap 3 siklus menstruasi. Pasien yang memiliki keluhan satu atau dua gejala nyeri dengan skor VAS ≥ 4 diberikan DLBS1442 sebanyak 3 x 100 mg sehari selama 12 minggu. Penurunan skor VAS diperoleh pada siklus pertama menstruasi pascapengobatan (sekitar 5,3 minggu setelah inisiasi pengobatan) dan penurunan skor VAS terus berlanjut setelah melewati 2 siklus terakhir pengobatan. DLBS 1442 efektif dalam mengatasi masalah nyeri pada endometriosis dan/ atau adenomiosis.

Kata Kunci: *DLBS 1442, dismenorea, endometriosis, adenomiosis*

Introduction

Endometriosis is a chronic inflammatory disease characterized by the presence of endometrium-like tissue outside the uterine cavity.[1] Gynecological disorders are estimated to occur in 176 million women worldwide and in one of 10 women of reproductive age.[2,3] Women with endometriosis commonly experience reduced quality of life due to pain symptoms, including premenstrual pain, dysmenorrhea, dysuria and dyschezia. The pain may continue for many years and may cause physical weakness as well as psychological, social and functional disability.[4,5]

The pathogenesis and pathophysiology of endometriosis is not fully understood. However, overexpression of estrogen receptor-b (ER-b) in endometriosis tissue is thought to contribute to the initiation and progression of endometriosis-related pain.[6] Increased expression of ER-b will in turn suppress the expression of estrogen receptor-a (ER-a), increasing the ER-b/ER-a ratio. Overexpression of ER-b also induces the suppression of the progesterone receptor and stimulates cyclooxygenase-2 (COX-2) activity, contributing to progesterone resistance and an inflammatory reaction.[7] Based on these findings, drugs that regulate ER-b and maintain the normal ER-b/ER-a ratio are promising potential therapies to prevent the progesterone resistance and inflammation associated with endometriosis-related pain.

DLBS1442 is a proprietary and standardized bioactive extract of *Phaleria macrocarpa*, an Indonesian medicinal plant natively known as 'mahkota dewa' (the crown of god). In a previous pre-clinical study, DLBS1442 demonstrated a capacity to down-regulate ER-b, COX-2 and phospholipase-A2 (cPLA2) gene expression. DLBS1442 was also demonstrated *in-vitro* up-regulation of progesterone receptor gene expression.[8,9] A previous clinical study by Tjandrawinata et al[9] showed that DLBS1442 was well-tolerated by subjects with pre-menstrual syndrome and was effective in relieving dysmenorrhea, abdominal pain and other symptoms related to premenstrual syndrome. Based on those findings, we conducted this case study to assess the effectiveness of DLBS1442 as a treatment of choice for pain related to endometriosis and/ or adenomyosis as primarily measured by the VAS.

Methods

We observed 10 consecutive patients presenting for treatment at Yasmin Infertility Clinic Dr. Cipto Mangunkusumo General Hospital Jakarta during January - March 2013. Selected patients were between 18-45 years old, not pregnant or breast-feeding and had not used hormonal contraceptives within the last three months. The patients' chief complaint was pain during their menstrual periods (i.e., dysmenorrhea), which could be accompanied by pre-menstrual pain, dysuria and/or dyschezia. All the patients have history of endometriosis and/ or adenomyosis surgery within 2 years. Transvaginal ultrasonography (ALOKA™, Pro-Sound SSD 3500 plus), a relatively effective and practical diagnosing tool for endometrioma and/ or adenomyosis was performed on the 10 patients. Patients did not have any plan to receive laparoscopy or other surgeries in the next 12 weeks.

After the diagnosis was confirmed, patients were asked to rate their pain on the 10 point VAS, with zero indicating an absence of pain and 10 indicating the most severe pain. Patients reporting one or more pain symptoms with a VAS score ≥ 4 were given 100 mg of DLBS1442 three times daily for 12 weeks. The VAS score for each pain symptom was evaluated at each of the next three menstrual cycles.

Results

Of the 10 patients (21-42 years old), two patients were diagnosed with adenomyosis and eight patients were diagnosed with endometrioma measuring 3 - 8 cm in diameter (Table 1).

Table 1. Duration of VAS Reduction of Dysmenorrhea

Initial Patient	Age (years)	Diagnosis	Duration of reduction of dysmenorrhea symptoms on the VAS
1	29	Endometrioma	4 weeks
2	37	Endometrioma	6 weeks
3	40	Adenomyosis	6 weeks
4	31	Endometrioma	7 weeks
5	37	Endometrioma	5 weeks
6	38	Adenomyosis	4 weeks
7	21	Endometrioma	8 weeks
8	25	Endometrioma	2 weeks
9	35	Endometrioma	7 weeks
10	42	Endometrioma	4 weeks

Pain scores on the VAS were found to decrease during the first post-treatment menstrual cycle and continued to decline with each subsequent menstrual cycle. On average, decline in dysmenorrhea pain as measured by VAS score started 5.3 weeks after the initiation of DLBS1442 treatment.

After 12 weeks of DLBS1442 treatment, the median VAS score for dysmenorrhea was reduced from baseline by 4.5 points, while scores for pre-menstrual pain, menstrual dyschezia and menstrual dysuria were reduced from baseline by 2, 1 and 0.5 points respectively (Table 2). The decline in VAS score for each pain symptom is demonstrated in Figure 1.

Table 2. Reduction in Each Pain Symptom on VAS during Three Menstrual Cycles

Type of pain	VAS (median) n = 10				Median reduction in VAS score per cycle over three menstrual cycles (Min-Max)
	Before treatment with DLBS1442 (Min-Max)	After treatment with DLBS1442			
		Cycle 1 (Min-Max)	Cycle 2 (Min-Max)	Cycle 3 (Min-Max)	
Dysmenorrhea	6.5 (4-10)	5 (1-8)	3 (0-8)	2 (0-3)	5 (3-8)
Pre-menstrual	2 (0-10)	0 (0-9)	0 (0-5)	0 (0-5)	1 (0-10)
Dyschezia	1 (0-9)	0 (0-1)	0 (0-0)	0 (0-0)	1 (0-9)
Dysuria	0.5 (0-6)	0 (0-6)	0 (0-2)	0 (0-0)	0.5 (0-6)

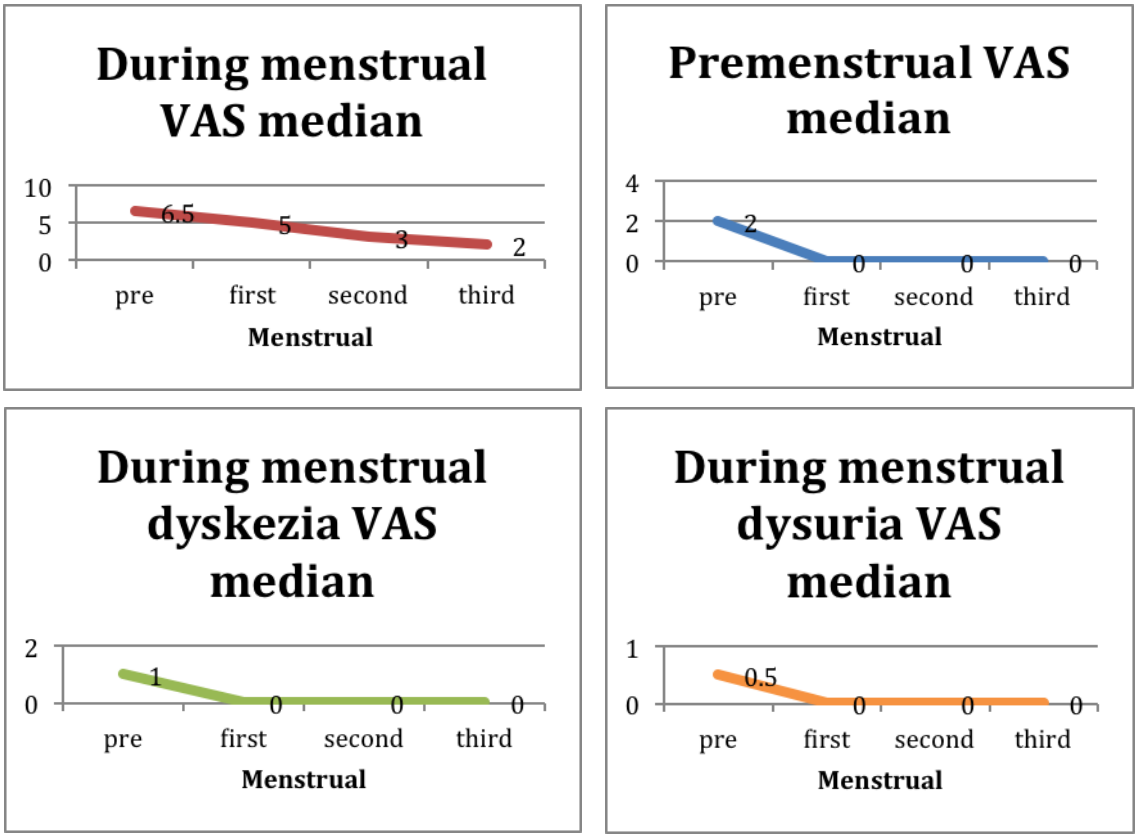

Figure 1. After DLBS1442 treatment, VAS scores for each pain symptoms decreased in the first menstrual cycle and continued to decline during the second and third cycles.

Discussion

Medical management of endometriosis primarily aims to delay disease progression and alleviate symptoms. Aside from infertility, the most debilitating symptom in women with endometriosis is pain manifested as severe dysmenorrhea, dyspareunia, chronic pelvic pain, dysuria or dyschezia. These symptoms also tend to worse with repeated menstrual cycles.[10,11] Therefore, pain relief has been one of the major goals of therapies for endometriosis. The most widely utilized treatment modalities are expectant management, surgery, and hormonal therapy.[12] Hormonal therapy is widely used, as endometriosis is an estrogen-dependent condition.[10] For endometriosis-associated pain, standard first-line medical therapies include non-steroidal anti-inflammatory drugs (NSAIDs), oral contraceptive (combination estrogens/progestins) or progestogens (*e.g.,* medroxyprogesterone acetate and norethisterone).[1-3,13,14] Failing these therapies, danazol or GnRH-analogue therapy (goserelin, nafarelin, buserelin, leuprorelin) is indicated, preferably in combination with simultaneous addition of estrogen–progestogen add-back therapy. However, if the physician believes that laparoscopy is required to confirm or reestablish the diagnosis, then operative laparoscopy with elimination of visible endometriotic implants is advisable.[14]

Although most patients receiving currently available medical therapy report symptomatic improvement (pain relief) and disease regression, recurrence rates and adverse events are still relatively high.[12,18] Such medical therapies are also ineffective in improving fertility rates. Hormonal-based treatment will further delay conception as they induce hormonal imbalances. The aim of hormonal drug therapy is to reduce estrogen levels, shutting down the normal hormonal cycle of stimulation and bleeding. When in a hypo-estrogenic state, the endometrial deposits shrink down and become inactive. Thus, hormonal medication suppresses but does not remove endometriosis and is effective only for short term management of symptoms. Active endometriosis returns gradually over one to two years after cessation of drug therapy.[12,15-18]

Vercellini et al showed that continuous use of a combined oral contraceptive pill for 24 months effectively reduced endometriosis-related pain intensity by 45.95% in patients with endometriosis.[17] Progestin-only pills effectively alleviated endometriosis-related pain and reduced recurrence rate after surgical treatment with no significant difference in results compared with combined oral contraceptive therapy.[18]

Additionally, Strowitzki et al[19] showed that treating patients with endometriosis with a regimen of dienogest 2 mg / day for 24 weeks led to a reduction in the mean VAS pain score by 4.75. Similarly, a reduction of 4.6 in VAS pain score was reported in patients receiving a regimen of 3.75 mg of leuprolide acetate depot treatment every four weeks. As high as a six-point reduction on VAS for endometriosis-related pain was reported by Petta et al[20] in a study using levonorgestrel-releasing intrauterine (LNG-IUS) therapy for six months. However, this method should not used in women who have never had sexual intercourse. [20]

Non-steroidal anti-inflammatory drugs have widely been studied for the treatment of dysmenorrhea and are proven to be effective through inhibition of cyclooxygenase.[21] However, NSAIDs have significant adverse reactions, including gastric ulcer and the potential to cause an anti-ovulatory effect when taken mid-menstrual cycle.[1,21,22]

Given the available literature on this topic, it is necessary to search for a novel agent with high efficacy in alleviating endometriosis-related symptoms, a relatively more desirable safety profile and more durable effectiveness. In this study, DLBS1442 demonstrated its effectiveness in reducing endometriosis and/ or adenomyosis associated pain. It is likely that DLBS1442 exerts it effects through triple mechanisms of action as demonstrated in a previous *in-vitro* study, i.e. by down-regulating the gene expression of ER-b, COX-2 and phospholipase-A2 (cPLA2) and up-regulating progesterone receptor gene expression.[8,9] Through these mechanisms, DLBS1442 with its anti-inflammatory activity can reduce endometriosis and/ or adenomyosis-associated pain without inducing a systemic hypo-estrogenic state. Therefore, no patients in this study reported adverse effects related to hormonal imbalance, such as disturbed menstrual cycles, flushing or weight gain. The promising results of this case study justify further larger clinical studies to confirm the efficacy of DLBS1442 in suppressing endometriosis-associated pain as well as in delaying disease progression in patients with endometriosis and / or adenomyosis.

Conclusion

This case study showed that a regimen of 100 mg of DLBS1442 three times daily in patients with endometriosis and or adenomyosis was effective in alleviating disease-related pain as demonstrated by early reduction in VAS scores for dysmenorrhea, pre-menstrual pain, menstrual dyschezia and dysuria. The pain intensity declined continuously with each subsequent menstrual cycle.

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