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Comparing the Efficacy in Reducing Pelvic Pain Score at 3 Months after Treatment in Clinically Diagnosed Endometriotic Patients between Leuprolide Acetate and Depot Medroxyprogesterone Acetate: A randomized controlled trial

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ABSTRACT

Objectives: To compare the efficacy of 11.25 mg-leuprolide acetate (Enantone L.P.) and 150 mg-intramuscular depot medroxyprogesterone acetate (DMPA-IM) (Depo-Progesta) in the reduction of pelvic pain score, satisfaction of the patients after 3 months of treatment and associated side effects.

Materials and Methods: The study design was based on a randomized controlled trial, which was conducted in thirty-six patients who attended gynecologic outpatient department at Her Royal Highness Princess Maha Chakri Sirindhorn Medical Centre (MSMC). These patients were randomized into two groups, either the 11.25 mg-leuprolide acetate or the DMPA-IM group at their first visit. The pelvic pain scores were gathered by using the numerical rating scale at their first visit and 3 months after treatment. The satisfaction score was gathered by using rating scale 1-10. Side effects were collected data as yes or no. Mann-Whitney U test was used to evaluate both the efficacy through the improvements in pelvic pain score and patient's satisfaction score. Finally, Chi-square test was used to evaluate side effects of both medications.

Results: The efficacy to reduce the pelvic pain score was similar between the 11.25 mg- leuprolide acetate and DMPA-IM group after 3 months of treatment. After the treatment, pain score was reduced from 7.00 (6.00, 8.00) [median (interquartile range)] to 2.00 (0.00, 2.00) in leuprolide acetate group and from 8.50 (6.00, 10.00) to 2.00 (2.00, 3.00) in the DMPA-IM group. The median (interquartile range) reduction in pain score was 73.21% (55.56, 100.00) in leuprolide acetate group and 71.43% (60.00, 80.00) in DMPA-IM group. However, this reduction did not show statistical significance between groups. Concerning the secondary objectives of this study, the median (interquartile range) of satisfaction score was 9.00 (7.00, 10.00) in leuprolide acetate group and 8.00 (8.00, 9.00) in DMPA-IM group at 3 months after treatment which were considered high but were not statistically significant between groups. In this study hot flashes were more commonly experienced by the patients in the leuprolide acetate group with statistical significance. In contrast, vaginal spotting was more common in patients of the DMPA-IM group.

Other side effects such as night sweat, mood swing and vaginal dryness experienced by these patients were not statistically different between groups.

Conclusion: This double-blinded randomized controlled trial demonstrated that 11.25 mg-Leuprolide acetate was as effective as 150 mg-DMPA-IM in terms of reduction in endometriosis-related pain and patient satisfaction at 3 months after the initial treatment without significant differences.

Keywords: leuprolide acetate, depot medroxyprogesterone acetate, endometriosis.

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การเปรียบเทียบประสิทธิภาพการลดอาการปวดในผู้ป่วยโรคเยื่อบุโพรงมดลูกเจริญผิดที่ ที่ 3 เดือนหลังการใช้ยา Leuprolide acetate และ Depot medroxyprogesterone acetate

อัครพัฒน์ โสวรรณกุล, พัชรินทร์ เกียรติสารพิภพ, กิตติพงษ์ คงสมบูรณ์

บทคัดย่อ

วัตถุประสงค์*: เพื่อเปรียบเทียบประสิทธิภาพในการลดอาการปวดจากโรคเยื่อบุโพรงมดลูกเจริญผิดที่ ที่ 3 เดือนหลังการรักษา และเพื่อเปรียบเทียบผลข้างเคียงที่เกิดขึ้นระหว่างการใช้ยาและความพึงพอใจของผู้ป่วยหลังได้รับการรักษาโรคเยื่อบุโพรงมดลูกเจริญผิดที่ด้วยยา Leuprolide acetate 11.25 mg (Enantone L.P.) และยา Depot medroxyprogesterone acetate 150 mg (Depo-Progesta)*

วัสดุและวิธีการ*: เป็นการศึกษาแบบ double blind prospective randomized controlled trial โดยเก็บข้อมูลจากผู้ป่วย 36 คน ที่มารับการรักษาที่คลินิกนรีเวช โรงพยาบาลศูนย์การแพทย์สมเด็จพระเทพรัตนราชสุดาฯ สยามบรมราชกุมารี โดยผู้ป่วยจะได้รับการสุ่มแบ่งออกเป็นสองกลุ่ม โดยกลุ่มที่หนึ่งจะได้รับยา Leuprolide acetate 11.25 mg (Enantone L.P.) และกลุ่มที่สอง Depot medroxyprogesterone acetate 150 mg (Depo- Progesta) คะแนนความปวดบริเวณท้องน้อยจะถูกบันทึกโดยใช้ Numerical rating scale ก่อนการรักษาและที่สามเดือนหลังการรักษา คะแนนความพึงพอใจใช้ rating scale 1-10 และผลข้างเคียงที่เกิดขึ้นเก็บข้อมูลเป็นใช่และไม่ใช่ จากนั้นนำข้อมูลคะแนนความปวดและความพึงพอใจมาคำนวนทางสถิติมาคำนวณทางสถิติเพื่อเปรียบเทียบหาประสิทธิภาพโดยใช้ Man-whitney U test และผลข้างเคียงที่เกิดขึ้นระหว่างการใช้ยา ใช้ Chi-square test*

ผลการศึกษา*: ประสิทธิภาพในการลดอาการปวดในผู้ป่วยสองกลุ่มไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ โดยในกลุ่ม Leuprolide acetate 11.25 mg (Enantone L.P.) มีค่ามัธยฐาน (ค่าพิสัยระหว่างควอไทล์) ของคะแนนความปวดลดลงจาก*

7.00 (6.00, 8.00) เป็น 2.00 (0.00, 2.00) โดยคิดเป็น 73.21% (55.56, 100.00) และในกลุ่ม Depot medroxyprogesterone acetate 150 mg mg (Depo- Progesta) คะแนนความปวดลดลงจาก 8.50 (6.00, 10.00) เป็น 2.00 (2.00, 3.00) โดยคิดเป็น 71.43% (60.00, 80.00) และคะแนนความพึงพอใจที่ 3 เดือนหลังการรักษา ในกลุ่ม Leuprolide acetate 11.25 mg (Enantone L.P.) มีค่ามัธยฐาน (ค่าพิสัยระหว่างควอไทล์) ของคะแนน 9.00 (7.00, 10.00) และในกลุ่ม Depot medroxyprogesterone acetate 150 mg mg (Depo-Progesta) มีคะแนน 8.00 (8.00, 9.00) ซึ่งมีคะแนนจัดอยู่ในระดับสูงทั้งสองกลุ่ม และไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ในเรื่องผลข้างเคียงจากการใช้ยาพบว่าในกลุ่ม Leuprolide acetate 11.25 mg (Enantone L.P.) พบอาการร้อนวูบวาบมากกว่าอย่างมีนัยสำคัญทางสถิติ และในกลุ่ม Depot medroxyprogesterone acetate 150 mg mg (Depo-Progesta) พบเลือดออกกะปริดกะปรอยทางช่องคลอดมากกว่าอย่างมีนัยสำคัญทางสถิติ โดยผลข้างเคียงอื่นๆ เช่น เหงื่อออกกลางคืน, อารมณ์แปรปรวน และช่องคลอดแห้ง ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ

***สรุป**: ประสิทธิภาพในการลดอาการปวดท้องน้อยหลังการใช้ยา Leuprolide acetate 11.25 mg (Enantone L.P.) และยา Depot medroxyprogesterone acetate 150 mg mg (Depo-Progesta)ที่สามเดือนหลังเริ่มต้นการรักษา ในผู้ป่วยโรคเยื่อบุโพรงมดลูกเจริญผิดที่ไม่มีความแตกต่างกันอย่างมีนัยสำคัญ*

***คำสำคัญ**: ยา Leuprolide acetate, ยา Depot medroxyprogesterone acetate, เยื่อบุโพรงมดลูกเจริญผิดที่*

Introduction

Endometriosis is one of the most common and troublesome gynecological diseases experienced by females of reproductive age. It is generally known as a chronic condition in which the endometrial tissue grows outside the endometrial cavity. The tissue usually seeds within the pelvic cavity, such as pelvic viscera, pelvic organs and the peritoneum[1,2]. Extra-pelvic endometriosis is less common; however, it could present in the lungs, brain, and gastrointestinal tract[2]. Symptoms commonly found in patients include dysmenorrhea, pelvic pain and infertility. The incidence is approximately 70-90% of those who are presented with pelvic pain[3]. However, the clinical presentation is quite inconsistent, with some patients experiencing severe symptoms while the others have little to no symptom. Generally, endometriosis could be diagnosed clinically in patients presenting with progressive dysmenorrhea, chronic pelvic pain, dyspareunia and infertility[4-6]. Many institutes advocate treatment of patients who are clinically diagnosed in order to decrease the percentage of those with subsequent complications[7]. Apart from those with surgical indication or those with fertility desire, the mainstay of treatment is medical intervention. There is no evidence as to which regimen is the most superior. Treatment is often personalized by patient's compliance and response to treatment, drug tolerance, and financial status. Examples of hormonal treatment are progestogen, anti-progestogen and gonadotropin releasing hormone agonist (GnRH agonist)[7, 8].

Progestogen has anti-endometriotic effects. It triggers endometrial decidualization which consequently leads to gradual endometrial thinning. However, its downside may be vaginal spotting, weight gain and delayed return of ovulatory function[1,2,7,9]. GnRH agonist, on the other hand, provides non-pulsatile stimulation to the hypothalamus, and thereby decreases estrogen level through inhibiting luteinizing hormones and follicle stimulating hormones production[1,2,10,11]. Furthermore, it can also reduce adhesion formation by decreasing plasminogen activator and matrix metalloproteinase activities[1,12]. Since the inhibition occurs at the top of the hormonal cascade, GnRH induces a state of reversible pseudomenopause which may effectively cause regression of endometriotic lesions. However, patients may experience several symptoms mimicking true menopause with an increased risk of osteoporosis after 6 months use[2].

In most public hospitals in Thailand, the most commonly used medical treatment of endometriosis are depot medroxyprogesterone acetate (DMPA) and leuprolide acetate[13]. Although DMPA appears to be a cost-effective choice, leuprolide acetate or GnRH agonist is believed to have a greater potency in reducing estrogen level and causes better regression of endometriotic lesions due to its efficacy to reduce estrogen level more than DMPA.

The primary objective of this study was to compare the efficacy of 11.25 mg-leuprolide acetate and 150 mg-intramuscular depot medroxyprogesterone acetate (DMPA-IM) in the reduction of pelvic pain score at 3 months after initial treatment. Moreover, the secondary objectives were to compare satisfaction of the patients at 3 months after initial treatment and associated side effects during 3 months of treatment.

Materials and Methods

This study was conducted as a prospective, double-blinded, randomized controlled trial in clinically diagnosed endometriotic patients attending gynecologic out-patient department (OPD) at HRH Princess Maha Chakri Sirindhorn Medical Center (MSMC) during July 2019 to September 2020. This study was approved by the institute's ethics committee (registration number SWUEC/F-436/2561).

In this study, the sample size was estimated from pilot study that showed mean of pain score after treatment as 1.14 & 2.29 and standard deviation as 2.29 with two-tail test, with an alpha-error of 5%, 90% power and ratio of 1:1. Therefore, the number of participants in study were 18 in each group.

The target population were those presented with pelvic pain or dysmenorrhea without being clinically diagnosed with endometriosis. We included patients with history and physical examination which suggest endometriosis. The inclusion criteria were the presence of clinically diagnosed endometriosis-associated pelvic pain over at least 6 months in females between the age of 18 to 49, which was defined as progressive dysmenorrhea, non-cyclical chronic pelvic pain and deep dyspareunia, with progressive dysmenorrhea as the main chief complaint. To diagnose the patients, clinical examination was done which included inspection of the vagina using a speculum especially at posterior fornix of vaginal wall, bimanual and rectovaginal palpation to search for infiltration or nodules of the vagina, uterosacral ligaments or pouch of Douglas, and detection of any painful induration. Transvaginal ultrasound was used to find the ovarian endometrioma and to rule out other diagnoses such as adenomyosis, myoma uteri or adnexal mass that may cause symptoms mimicking those of endometriosis. The exclusion criteria included pregnancy, continuous use of hormonal therapy and medical diseases including diabetes mellitus, dyslipidemia, venous thrombosis, coronary artery disease, stroke, epilepsy, osteoporosis, chronic liver disease. In addition, those with a history of breast or gynecologic malignancy which could be stimulated by hormone and those with undiagnosed abnormal uterine bleeding were also excluded. More specific to the medications used in this study, patients with a history of hypersensitivity to DMPA or leuprolide acetate (i.e. urticaria, puffy eyelids or respiratory distress), and those that cannot tolerate side effect of the drugs such as hot flashes or vaginal spotting. Finally, those with fulfilled indications for surgical management or cases which pathological tissue was required due to inability to rule out malignancy were excluded as well.

Patients who agreed to participate provided a signed informed consent upon recruitment and were asked to complete a questionnaire evaluating the presence and severity of dysmenorrhea, deep dyspareunia and non-menstrual pelvic pain graded by a score of 0 to 10 using the numerical rating scale (NRS). In addition, information gained from physical examination including pelvic tenderness or induration were also recorded on the questionnaire. Subsequently, these patients underwent simple randomization to either 150 mg-DMPA-IM (Depo-Progesta 150 mg/3mL) or 11.25 mg-leuprolide acetate (Enantone L.P. 11.25mg), both via intramuscular route. Both the researchers and patients were blinded to the randomization. The patients were injected with these medications by a nurse at the gynecologic OPD and sent home after a short duration of observation for immediate side effects.

A follow-up by phone was done at 1 and 2 months after initial treatment and a follow-up visit of the patients included in this study was 3 months after the initial treatment. Severity of pain was reevaluated in the follow-up visit using the NRS. Satisfaction score was recorded as a grade based on a scale of 1 to 10. Finally, the side effects caused by the medications, for example, hot flashed, night sweats, mood swings, vaginal spotting and dryness were categorically recorded as either yes or no.

Thirty-nine patients (n = 39) were initially eligible for participation in which 3 patients were excluded from data analysis due to loss to follow-up, recently diagnosed cervical lesion and subsequently deny participating, and inability to tolerate side effects of leuprolide acetate. Therefore, thirty-six women (n = 36) were included in data analysis. All analyses were done using Stata version 15.1 (StataCorp. Stata statistical software: Release 15.1. College Station, TX: Stata Corporation, Texas, USA, 2017). Normality of data was tested before analysis using Shapiro-Wilk test. Continuous data between the two intervention groups were tested by independent t-test and Mann-Whitney U test for parametric, and non- parametric distribution, respectively. Chi square test or fisher exact test was used to test categorical data. All statistical analyses

were two-tailed, and the significance level of 0.05 was used. 95% confidence interval was calculated.

Results

After corresponding to the inclusion and exclusion criteria shown in Fig. 1, the demographic characteristics of the patients included in this study are shown in Table 1. The mean age was 33.44 ± 5.83 years in leuprolide acetate group and 33.11 ± 1.69 in DMPA-IM group. The median weight and BMI of patients were 56.00 (53.25, 61.60) kilograms and 22.00 (19.86, 24.52) kg/m^2 in leuprolide acetate group and 56.00 (53.25, 61.60) and 22.46 (21.33, 28.47) kg/m^2 in DMPA-IM group. The median scores of chronic pelvic pain and duration of symptoms of leuprolide acetate group were 7.00 (6.00, 8.00) and 12 months (6, 36), while those were 8.50 (6.00, 10.00) and 18 months (12, 36) for the DMPA-IM group. The two groups revealed no significant differences in these baseline characteristics.

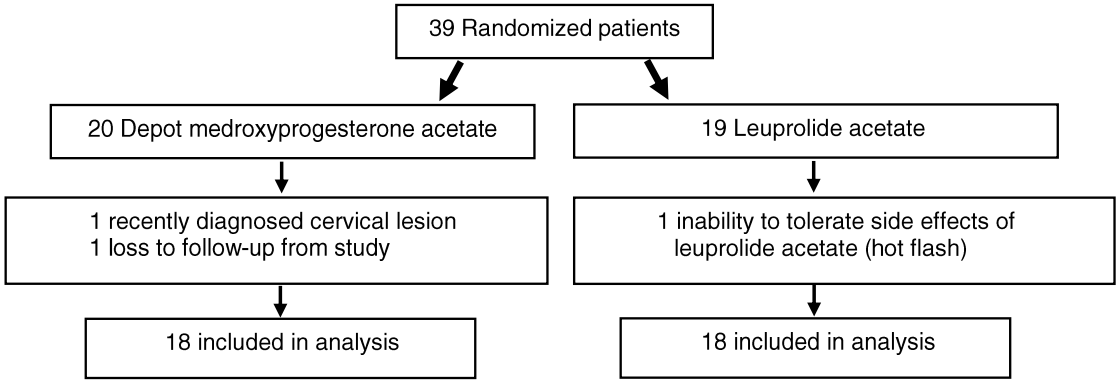

Fig. 1. Profile of patient follow-up following randomization to either depot medroxyprogesterone acetate or leuprolide acetate.

Table 1. Demographic characteristics.

Characteristic	Depot medroxyprogesterone acetate (n = 18)	Leuprolide acetate (n = 18)	p value
Age (year), mean ± SD	33.11±1.69	33.34±5.83	0.880*
Weight (kgs), median (IQR)	56.50 (47.50, 65.50)	56.00 (53.25, 61.60)	0.824**
BMI (kgs/m^2), median (IQR)	22.00 (19.86, 24.52)	22.46 (21.33, 28.47)	0.700**
Pelvic pain score, median (IQR)	8.50 (6.00, 10.00)	7.00 (6.00, 8.00)	0.082**
Duration(months), median (IQR)	18 (12, 36)	12 (6, 36)	0.471**

SD: standard deviation, IQR: interquartile range, BMI: body mass index
*Independent T-Test, ** Mann-Whitney U test

Pelvic pain scores after the initial treatment in both groups are shown in Table 2. After the treatment, pain score was reduced from 7.00 (6.00, 8.00) to 2.00 (0.00, 2.00) in leuprolide acetate group and from 8.50 (6.00, 10.00) to 2.00 (2.00, 3.00) in the DMPA-IM group at 3 months after treatment. Therefore, the pain score was significantly reduced from baseline in both groups. but were not different in terms of statistical significance between them.

Concerning the secondary objectives of this study, the satisfaction score was 9.00 (7.00, 10.00) in leuprolide acetate group and 8.00 (8.00, 9.00) in DMPA-

IM group at 3 months after treatment, which were not statistically significant between groups.

The associated side effects arising from both medications used during this study are shown in Table 3. Hot flashes were more commonly experienced by the patients in the leuprolide acetate group with statistical significance. In contrast, vaginal spotting was more common in patients of the DMPA-IM group. Other side effects such as night sweat, mood swing and vaginal dryness experienced by these patients were not statistically different between groups.

Table 2. Pelvic pain score after receiving medication.

Pelvic pain score	Depot medroxyprogesterone acetate median (IQR)	Leuprolide acetate median (IQR)	p value*
Baseline pain score	8.50 (6.00, 10.00)	7.00 (6.00, 8.00)	0.082
After 3 months	2.00 (2.00, 3.00)	2.00 (0.00, 2.00)	0.274
% Improvement after 3 months	71.43 (60.00, 80.00)	73.21 (55.56, 100.00)	0.274

IQR: interquartile range
*Mann-Whitney U test

Table 3. Side effect of medication.

Side effect of medication	Depot medroxyprogesterone acetate n (%)	Leuprolide acetate n (%)	p value*
Hot flash	11/18 (61.11)	14/18 (77.78)	0.018
Night sweat	11/18 (61.11)	12/18 (66.67)	0.729
Mood swing	11/18 (61.11)	10/18 (55.56)	0.735
Spotting	16/18 (88.89)	6/18 (33.33)	0.001
Vaginal dryness	7/18 (38.89)	10/18 (55.56)	0.317

*Chi-square test

Discussion

Based on this study, the cohort of population was selected based on the clinical diagnosis of endometriosis and its associated pain, primarily through history taking and physical examination. From the review of literature, the variety of presenting symptoms and its severity is usually not correlated with the type or size of endometriotic lesions found via diagnostic laparoscopy[6,11]. Currently, there are many treatment options of endometriosis including medical and surgical options. Medical treatment is a choice for patients who do not wish for pregnancy and require reduction in endometriosis-related pain. On the other hand, surgical option which is more invasive seems appropriate for patients who have fertility need and require reduction in pain. In this study, we aimed to compare two of the most commonly used medical treatments in practical management. Firstly, leuprolide acetate, its action to inhibit the hypothalamic-pituitary-ovarian axis and subsequent endometrial growth to menopausal-like state makes it an effective choice but its cost may prevent some patients from selecting this option. For DMPA-IM, it is commonly used in clinical practice because of its efficacy in reducing endometriosis-related pain, well-documented safety profile, and cost-effectiveness. The medications chosen in this study are those that are traditionally used to treat endometriosis-associated pain and have established a well-known

safety profile and efficacy comparable with surgical management[7-11].

In general, the medical treatments selected in this study are more cost-effective compared with surgery[13]. In fact, the mechanism of actions of these medications are to suppress endometrial proliferation and therefore are commonly used in the clinical setting of endometriosis[7-11]. Based on previous studies, the utilization of both depot medroxyprogesterone acetate and leuprolide acetate led to good clinical outcomes in terms of reducing endometriosis-related pain. From Crosignani, et al. result and in the same way Schlaff et al found that after administration of subcutaneous depot medroxyprogesterone acetate or leuprolide acetate every 3 months for a total of 6 months could reduce pain score at 6 and 18 months after treatment[14,15].

In this randomized, double-blinded controlled trial, leuprolide acetate was shown to be as effective as DMPA-IM in the reduction of endometriosis-associated pain at the follow-up of 3 months after treatment. Theoretically, endometriosis involves local estrogen production and subsequent activation of estrogen receptors which produces various cytokines such as interleukin (IL)-6, IL-8, tumor necrotic factor (TNF)-alpha[16]. From previous literature, leuprolide acetate acts by inhibiting the HPO axis, while progestins activates the pituitary progesterone receptors creating hypoestrogenic and hyperprogestrogenic systemic environment and possibly amenorrhea. However, recent studies also suggest that progestins act locally by inhibiting cytokines such as IL-6, IL-8 and TNF-alpha which is dependent on the expression of their target receptors in an inflammatory environment[17]. Although these medications work through slightly different mechanisms, their efficacy appears to be similar.

Based on this study, both leuprolide acetate and DMPA-IM led to good patient satisfaction with the score of 8-9 from 10. It is considered to be in high level because of reduction in pain score after treatment and associated side effect that can be tolerated. This finding was consistent with the previous literature from Crogsignani which found that the quality of life was greatly improved by using Endometriosis Health Profile-30 Questionnaire (EHP-30) and Short Form 36 Health Survey (SF-36 scales) as tools of measurement[14]. Patient satisfaction as measured by the scores was not statistically different between the two treatment groups. In terms of side effects, hot flashes were most commonly encountered in the leuprolide acetate group. Unfortunately, there was one participant (1/14, 7.14%) who could not tolerate the side effect and required an add-back hormonal therapy. In contrast, intermenstrual bleeding was more significantly reported in the DMPA-IM group. There was no participant who could not tolerate this side effect. These results were comparable with those found by Schlaff et al, in which the experience of side effects of vaginal dryness, mood swings and night sweats were not statistically different between groups[15]. In general, from the follow-up of patients concerning the side effects from the mediations, most participants could tolerate the side effects which correlated with the good satisfaction scores.

The overall results based on the primary and secondary objectives of this study showed that the efficacy of treatment and patient satisfaction in both arms were not significantly different. However, the side effects experienced by the participants and cost-effectiveness were different between the two groups. Therefore, these factors may guide the patient to select an appropriate treatment option in order to maximize its benefits.

The main strength of this study was the selection of patients who have never received medical or hormonal treatment which could have adversely affected the results. In addition, the double-blinded randomized controlled trial nature of this study enabled the production of clinical results which correlate closely with reality.

There are several limitations of this study. First, the insignificant results in this study may be caused from small sample size. Second, uneven normal distribution of data could make them unrepresentative of general population. Third, exclusion of information on the use of other medications for pain control during the study period could have adverse effects on the results. Fourth, follow-up by telephone call may lead to inaccurate information when compared with face-to-face interview. Last, as the endometriosis is a chronic

disease and requires long term management, this study provided only short-term follow-up.

Conclusions

This double-blinded randomized controlled trial demonstrated that 11.25 mg-Leuprolide acetate was as effective as 150 mg-DMPA-IM in terms of reduction in endometriosis-related pain and patient satisfaction at 3 months after the initial treatment without significant differences.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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