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Effect of DMPA on IL-1 Alpha in Serum of Women with Endometrioma

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ABSTRACT

Objective: To study the effect of DMPA on serum IL-1α in women with endometrioma undergoing the conservative surgery.

Materials and methods: A randomized clinical trial was performed in thirty-five women with endometrioma who underwent conservative surgery in Reproductive Endocrinology and Laparoscopy clinic in Department of Obstetrics and Gynecology, Faculty of Medicine Ramathibodi Hospital.

These patients were randomly assigned to one of the following treatments: group A surgery and postoperative treatment with DMPA 150 mg intramuscular or group B surgery alone. Serum IL-1α level was measured by enzyme-linked immunosorbent assay (ELISA) in both groups. Pain scores were evaluated using a visual analog scale (VAS) at 2 and 12 weeks after the operation.

Results: There was no significant difference in IL-1α serum levels between both groups at 2 weeks and 12 weeks after the surgery ($p = 0.06$ and 0.86 respectively). There was no significant difference in pre and postoperative IL-1α level between both group ($p = 0.23$ and 1.00 respectively). Pain scores of both groups were significantly decreased at 2 weeks and 12 weeks after the surgery ($p < 0.001$). The patients in DMPA group had significantly less pain scores at 12 weeks after the surgery ($p = 0.01$).

Conclusion: The current study demonstrated that no significant change of IL-1α serum level in women with endometrioma before and after the surgery, with or without postoperative treatment with DMPA. We found decreasing of pain score in both group after surgery and less pain score in DMPA group.

Keywords: endometriosis, endometrioma, conservative surgery, IL-1α, DMPA

Introduction

Endometriosis, the presence of endometrial-like tissue outside the uterus, is a disease associated with pelvic pain and infertility. It affects approximately 10% of women of reproductive age[1]. The etiology and pathogenesis of endometriosis is still unclear. Recent researches have shown that peritoneal fluid of women with endometriosis establishes a microenvironment for the development of the disease and undergoes a number of pathological changes. The microenvironment includes inflammation and immune dysfunction resulting in angiogenesis, adhesion and invasion of endometrial cells[2-5]. As for the inflammation, macrophage is the predominant type of cells in peritoneal fluid, which play a crucial role in the maintenance of humoral and cell-mediated immunity[6,7]. Activated peritoneal macrophages secrete several cytokines and growth factors, which involve in the pathogenesis of endometriosis. Studies indicated that the levels of macrophage-derived factors such as interleukin (IL), tumor necrosis factor-alpha (TNF-α), monocyte chemotactic protein-1 (MCP-1) and vascular endothelial growth factor (VEGF) in women with endometriosis are elevated[8-11].

Interleukin -1, mainly produced by macrophage and monocyte, is an important mediator that plays a key role in immune and inflammatory response in human. It induces secretions of the angiogenic factors (VEGF, IL-6, IL-8) and the intracellular adhesion molecule-1 (ICAM-1) leading to angiogenesis and adhesion. The IL-1 family consists of two distinct molecular forms, IL-1α and IL-1α which are encoded by different genes, but have comparable biological activities[12]. Studies showed the important role of the IL-1 family in endometrium related disorders including endometriosis[2, 3, 5, 10, 13]. It may promote the development of endometriosis in the peritoneal cavity by up-regulating the expression of other cytokines and growth factors[14]. Additionally, IL-1 is an important stimulator of expression and production in vitro of chemokines in endometrial stromal cells and macrophages of women with endometriosis[15,16].

Recent study has demonstrated an elevated levels of serum of IL-1α in the women with endometriosis[14].

Depot medroxyprogesterone acetate (DMPA), a well-tolerated, inexpensive and minimal metabolic side effect medication, has been used for contraception for a long time. Inhibition of ovarian function during DMPA use causes the endometrium to become thin and atrophic. This phenomenon could be also found in the ectopic endometrium[17, 18]. With this evidence, DMPA has been used in endometriosis treatment worldwide for 50 years[19]. Clinically, it can prevent the recurrence of the disease and symptoms preference. It is possible that DMPA plays a role in decreasing of inflammatory mediators from endometriotic lesions. Therefore, the aim of this study was to investigat the role of DMPA on the suppression of inflammation, using IL-1α as the marker, in the recurrent process of the disease after endometriotic cystectomy.

Materials and methods

This study was conducted between June, 2011 and January, 2012. It was approved by the Ethical Clearance Committee on Human Rights Related to Researches Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University. All women signed informed consent agreements.

Thirty-five Thai women with endometrioma were included in this study. All women had no previous ovarian surgery. None woman had used any hormonal medications for at least 3 months.

All women underwent history taking, physical examination, determination of systolic blood pressure (SBP), diastolic blood pressure (DBP), height, body weight. Body mass index (BMI) was calculated by BW in kilograms (kg) divided by height in meters squared (m^2) at the start and the end of treatment. The pain score was also evaluated by visual analog scale. Transvaginal ultrasonography (TVS) was used to evaluate pelvic organs before and after treatment in all women.

Baseline blood samples were obtained in the operative room during intravenous infusion on the day of surgery. The second sample was measured at 2

weeks postoperation and the third sample was measured at 12 weeks postoperation. These samples were centrifuged and separated immediately after collection. They were stored at -80°C until the analysis was performed.

Subsequently, all women with endometrioma were randomly allocated into two groups using the number randomized in blocks generated by computer. Eighteen women of group A underwent conservative surgery and received intramuscular DMPA 150 mg at 2 weeks after the operation. Seventeen women of group B underwent conservative surgery alone. Follow up visits were scheduled at 2 weeks and 12 weeks after the operation. At the end of treatment all patients were reevaluated for the same parameters as those before treatment.

Serum IL-1α was measured with enzyme-linked immunosorbent assay method, using commercially available kits (RayBio®). Analytical sensitivity was 2 pg/mL. The intra- and inter-assay coefficients of variances (CV) were < 10% and < 12% respectively.

Statistical Analysis

All analyses were performed using STATA version 12.0 software (Stata Corp., College Station, Texas, USA). Continuous data with normal distribution were presented as mean ± SD, whereas those without normal distribution as median (range). Categorical data were presented as number (%). Chi-square or Fisher exact test were used to compare characteristics between both groups. Basal parameters of the two groups were compared by t-test or Mann-Whitney U nonparametric test. IL-1α level and pain score of both groups were compared by Kruskal–Wallis test. Determination of treatment effects controlling for BMI at baseline, using the linear regression analysis. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 35 women with endometrioma were randomly assigned to two treatment groups, group A (n = 18) and B (n = 17). The complete treatment rate was 100%. Demographic and baseline characteristics of endometriosis patients are shown in Table 1. There was no significant differences in mean age, BMI, parity, type of surgery, rAFS staging, intraoperative finding of adenomyosis, IL-1α level and pain score.

The comparison of IL-1α levels in each group is shown in Table 2. There was no significantly difference in IL-1α level in both groups at 2 weeks and 12 weeks after the surgery (6.30±3.70 pg/ml vs. 4.27±3.90 pg/ml and 5.30±4.80 pg/ml vs. 5.80±5.10 pg/ml, p = 0.06 and 0.86 respectively). There were no significant difference in IL-1α levels at pre-operation and post-operation between both groups (p = 0.23 and 1.00, respectively), there as a trend toward decreasing of IL-1α level in DMPA group which nearly reach statistical significance at 12 weeks period (p = 0.06).

Furthermore, pain scores of both groups were significantly decreased at 2 weeks and 12 weeks after the surgery, patients in DMPA group had significantly less pain scores than in non-DMPA group at 12 weeks after the surgery (1.30±1.10 vs. 2.40±1.10, p=0.01) (Table 3).

Table 4 shows the adverse events of both groups. Most adverse events were more common in DMPA group, except headache. (p = 0.006). The most common side effects were intermenstrual bleeding and increase in body weight. No serious adverse events were reported.

Table 1. Clinical characteristics, before initiation of treatment

Characteristics	DMPA group N=18	Non-DMPA group N=17	p
Age (years.)	34.40±6.00	32.80±6.50	0.48
BMI (kg/m^2)	20.50±2.90	20.80±2.00	0.76
Parity			
0	12 (66.66%)	12 (70.59%)	1.00
1	5 (27.78%)	4 (23.53%)	
2	1 (5.56%)	1 (5.88%)	
Type of surgery			
Laparoscopy	16 (88.89%)	15 (88.24%)	0.90
Adenomyosis (intraoperative finding)	6 (33.33%)	6 (35.30%)	
rAFS staging			
stage III	6 (33.33%)	7 (41.18%)	0.12
stage IV	12 (66.67%)	10 (58.82%)	0.63
IL-1α levels (pg/ml)	8.75 (0.00-29.1)	5.95 (0.00-12.99)	0.06
Pain scores (VAS) mean (min-max)	9.50 (6.00-10.00)	8.00 (5.00-10.00)	0.13

Results are expressed as mean ± SD, mean (range) or n (%)

Table 2. Comparison of IL-1α levels in DMPA group and non DMPA group at preoperation, 2 and 12 weeks post operation

IL-1α levels (pg/ml)	Preoperation	2 weeks post operation	12 weeks post operation	p
DMPA group	10.00±8.00	6.30±3.70	5.30±4.80	0.23
Non DMPA group	5.69±4.20	4.27±3.90	5.80±5.10	
p-value	0.06	0.06	0.86	1.00

Results are expressed as mean ± SD

Table 3. Neonatal outcomes

Pain scores (VAS)	Preoperation	2 weeks post operation	12 weeks post operation	p
DMPA group	9.00±1.20	3.90±1.90	1.30±1.10	< 0.001
Non DMPA group	8.30±1.40	4.40±1.10	2.40±1.10	< 0.001
p-value	0.13	0.38	0.01	

Results are expressed as mean ± SD

Table 4. Adverse events during treatment

Adverse event	DMPA (N=18)	Non-DMPA (N=17)	p
Total Adverse event	16 (88.88%)	4 (22.22%)	0.006
Injection-site reaction	0 (0.00%)	0 (0.00%)	
Headache	1 (5.50%)	2 (11.80%)	
Increase body weight	7 (38.90%)	2 (11.80%)	
Libido decrease	1 (5.50%)	0 (0.00%)	
Intermenstrual bleeding	8 (44.40%)	0 (0.00%)	

Discussion

Peritoneal fluid contains a variety of cells, including macrophages, lymphocytes, ectopic endometrial implants or mesothelial cells, all of which can produce cytokines. Macrophages are attracted to the peritoneal environment more abundantly than any other cell type[20]. Disorders of peritoneal macrophage and peripheral blood monocyte function contribute to the pathogenesis of endometriosis[7]. However, the mechanism involved in the activation of these cells remains unknown. Increased levels of monocyte/macrophage-derived secretory products, such as cytokines, growth factors, reactive oxygen species or inflammatory mediators, are characteristic of endometriosis[2, 3, 5].

One of the macrophage secretory products, IL-1, plays an important physiological role in the microenvironmental of peritoneal cavity and in local intercellular interactions. Additionally, apart from macrophages other sources of IL-1 are the ectopic endometrial cells and mesothelial cells[5, 21]. Impairment of the IL-1 family cytokine network may be a cause of disorders in immune privilege in the peritoneal cavity of women with endometriosis.

IL-1 is a pleiotropic cytokine that plays an important role in the regulation of immune response and inflammation. It may promote the development of endometriosis in the peritoneal cavity by up-regulating the expression of other cytokines and growth factors. IL-1 is known to enhance IL-6 and TNF-α, important cytokines that are prognostic factors in the progression of endometriosis[9]. Additionally, IL-1 is an important stimulator of expression and production in vitro of chemokines in endometrial stromal cells and macrophages of women with endometriosis. IL-1 enhanced the expression of IL-8, growth-related oncogene-a (GRO-a) and epithelial neutrophil-activating peptide-78 (ENA-78)[15, 16]. IL-1α is also a potent stimulator of matrix metalloproteinase enzymes (MMPs) in the endometrium[22, 23].

Most studies found that there are positive correlation between IL-1α level in the peritoneum and serum of women with endometriosis and observed the presence of IL-1α in the serum of affected women with no detectable concentrations of this cytokine in healthy women[14, 24-26].

The administration of drugs reduced levels of IL-1α, In untreated endometriosis, the level of this cytokine was higher before than after danazol treatment and also in normal fluids. Moreover, Meresman et al[27] showed that the GnRH agonist also decreased IL-1 production in endometrial cell cultures from endometriosis patients. The GnRH agonist appears to have a direct effect on endometrial cell cultures by decreasing the release of pro-mitogenic cytokines, such as IL-1[27]. Both ectopic and eutopic endometrial cells of women with endometriosis show an increased sensitivity to IL-1 in vitro[28, 29]. This suggests that endometrial epithelial cells from women with endometriosis have the inherent property of being more sensitive to proinflammatory stimuli and may display excessive inflammatory response[14].

In this study, we measured the concentrations of IL-1α level in the serum. We observed that the baseline IL-1α level was comparable with most studies (10.00±8.00 pg/ml in DMPA group and 5.69±4.20 pg/ml in non-DMPA group) and the level slightly decreased after the surgery, however, it was not statistically significant (10.00±8.00 to 6.30±3.70 pg/ml in DMPA group and 5.69±4.20 to 4.27±3.90 pg/ml in non DMPA group). Decreasing rate of IL-1α is not equal to healthy women (<0.50 pg/ml in most of the studies). This information may be explained by these reasons. First, the surgical treatment in most patients was cystectomy; therefore it was not possible to improve all the inflammatory process in endometriosis patients. Second, we found adenomyosis in one third of the participants, which might have an effect on IL-1α level in the patients, however there were no previous studies in this field.

Twelve weeks after the operation, we found the decreasing levels of IL-1α only in DMPA group, however the difference did not reach statistical significance (10.00±8.00 pg/ml to 5.30±4.80 pg/ml, p=0.23 in DMPA group and 5.69±4.20 pg/ml to 5.80±5.10 pg/ml, p=1.00 in non-DMPA group). According to decreasing rate of IL-1α, we found nearly significant in decreasing rate at 12th weeks postoperation in DMPA group (p=0.069), This suggests that DMPA may have some property of decreasing proinflammatory stimuli and may influence excessive inflammatory response in endometriosis women. But in this study, the period of DMPA administration was only 12 weeks and the results shown very wide standard deviation so we need more participants and longer time to demonstrate the relationship between inflammatory response and DMPA.

In the aspect of pain response, we found significant decrease in pain scores at 2 weeks and 12 weeks post operation in both groups (9.00±1.20 to 3.90±1.90 to 1.30±1.10, p<0.001 in DMPA group, 8.30±1.40 to 4.40±1.1 0 to 2.40±1.10, p<0.001 in non-DMPA group) At the 12th weeks, the pain score in DMPA group was less than non-DMPA group, although not clinically significant but this suggested that postoperative medical treatment constitutes an important alternative or complement to surgery in decreasing pain. We need more time to investigate the response of DMPA in the aspect of alteration of recurrence of pain or disease. In the review of the effect of oral contraceptives (OCs) and progestins in the controlled trials on the treatment of symptomatic endometriosis (1990-2010)[30], it showed the benefit of prolong injected progestin in this aspect, which was different from the conclusion of ESHRE guideline in 2005.

The strength of this study is that it is the first study that investigates the effect of DMPA on inflammatory response, represented by IL-1α level. The IL-1α level can be determined by blood sampling which is a non-invasive test and is not affected by the period of the cycle. It is a randomized controlled trial that blinded the investigators who examined the IL-1α level, and all sample were analysis at the same time to avoid the variability of the kit.

The limitation of this study is that there was no control group and all samples were from patients with advanced stage (III, IV) endometriosis, so these results cannot be extrapolate to all stages of endometriosis.

Although the level of serum IL-1α was not significantly decrease after post-operative DMPA treatment but the decreasing level tended to be significant so we expected that if we administer DMPA at a longer time, such as at 6 or 12 months, IL-1α level might be significantly decreased.

These study demonstrated that there was no significant change of IL-1α level in women with endometrioma before and after the surgery, with or without postoperative treatment with DMPA. We found a decrease in pain scores in both groups after the surgery especially in DMPA group at 12 weeks postoperation.

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ผลของ DMPA ต่อ interleukin 1 alpha ในเลือดของผู้ป่วยโรคเยื่อบุมดลูกเจริญผิดที่

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วัตถุประสงค์ : *เพื่อศึกษาผลของยา DMPA ต่อระดับของ interleukin-1 alpha ในเลือดของผู้ป่วยโรคเยื่อบุมดลูกเจริญผิดที่*

รูปแบบการวิจัย : *การวิจัยเชิงทดลองแบบสุ่ม และมีกลุ่มควบคุม*

สถานที่ทำวิจัย : *คลินิกรักษาผู้ป่วยโรคทางต่อมไร้ท่อและหน่วยผ่าตัดส่องกล้อง ภาควิชาสูติศาสตร์-นรีเวชวิทยา คณะแพทยศาสตร์ โรงพยาบาลรามาธิบดี*

กลุ่มตัวอย่าง : *ผู้ป่วยโรคเยื่อบุมดลูกเจริญผิดที่ 35 คน สุ่มเป็น 2 กลุ่ม โดยใช้คอมพิวเตอร์ กลุ่ม A จำนวน 18 คน ได้รับการรักษาด้วยการผ่าตัดร่วมกับให้ยาฉีด DMPA 2 สัปดาห์หลังผ่าตัด กลุ่ม B ได้รับการรักษาด้วยการผ่าตัด*

วิธีการทำวิจัย : *ผู้ป่วยทุกคนจะได้รับการเก็บตัวอย่างเลือดเพื่อหาระดับของ Interleukin-1 alpha ร่วมกับให้ประเมินระดับความเจ็บปวดก่อนผ่าตัดและหลังผ่าตัด เมื่อเวลา 2 และ 12 สัปดาห์ ตามลำดับ*

ตัววัดที่สำคัญ : *ระดับของ IL-1 alpha ที่วัดระดับโดยใช้เทคนิค ELISA, ระดับความเจ็บปวดหลังผ่าตัด*

ผลการวิจัยระหว่างการศึกษา : *ไม่มีสตรีคนใดขอออกจากการศึกษา และสตรีทั้งสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติในแง่ของข้อมูลพื้นฐาน พบว่าระดับของ IL-1α ของสตรีทั้งสองกลุ่ม เมื่อเปรียบเทียบระหว่างก่อนผ่าตัดและหลังผ่าตัดที่เวลา 2 สัปดาห์ และ 12 สัปดาห์ ไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (6.30±3.70 vs. 4.27±3.90 and 5.30±4.80 vs. 5.80±5.10 p=0.06, 0.86 ตามลำดับ) และเมื่อเปรียบเทียบระดับของ IL-1α ระหว่างกลุ่มที่ได้รับยา DMPA และไม่ได้รับยาแล้ว ก็พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติเช่นกัน ทั้งเมื่อก่อนผ่าตัด หลังผ่าตัด ที่เวลา 2 สัปดาห์ และ 12 สัปดาห์ (p=0.23, 1.00 ตามลำดับ) แต่อย่างไรก็ตาม พบความแตกต่างอย่างมีนัยสำคัญในแง่ของการลดลง ความเจ็บปวดในทั้ง 2 กลุ่ม รักษาทั้งที่เวลา 2 สัปดาห์ และ 12 สัปดาห์ เมื่อเทียบกับก่อนผ่าตัด โดยพบว่ากลุ่มที่ได้รับยา DMPA หลังการผ่าตัดนั้นมีความเจ็บปวดลดลงมากกว่ากลุ่มที่ไม่ได้รับยา และพบว่าความแตกต่างนี้เริ่มมีนัยสำคัญทางสถิติเมื่อ 12 สัปดาห์หลังผ่าตัด (1.30±1.10, 2.40±1.10, p=0.01) พบอาการข้างเคียงจากยามากกว่าอย่างมีนัยสำคัญทางสถิติ ในกลุ่มที่ได้รับการรักษาด้วย DMPA (p=0.006) โดยอาการข้างเคียงจากยาที่พบมากที่สุดได้แก่ อาการเลือดออกกะปริดกะปรอย และน้ำหนักเพิ่มขึ้น แต่อย่างไรก็ตามเป็นอาการข้างเคียงจากยาที่ผู้ป่วยยอมรับได้*

สรุป : *การศึกษานี้แสดงให้เห็นว่าไม่พบการเปลี่ยนแปลงของระดับของ IL-1α ในผู้ป่วยโรคเยื่อบุมดลูกเจริญผิดที่ทั้งก่อนและหลังผ่าตัดรักษาที่เวลา 2 และ 12 สัปดาห์ ไม่ว่าจะได้รับการรักษาด้วย DMPA หลังผ่าตัดหรือไม่ก็ตาม แต่ในแง่ของอาการเจ็บปวดหลังผ่าตัด พบว่ามีการลดลงอย่างมีนัยสำคัญทางสถิติ หลังผ่าตัดรักษาทั้งที่เวลา 2 และ 12 สัปดาห์ โดยพบว่ามีการลดลงของความเจ็บปวดมากกว่าในกลุ่มที่ได้รับยา DMPA หลังผ่าตัด ซึ่งเริ่มพบว่ามีความต่างกันอย่างมีนัยสำคัญทางสถิติเมื่อ 12 สัปดาห์หลังผ่าตัด*