대한폐경회지 제11권 제2호 2005
Vol. 11 No. 2 Jun. 2005

The Clinical Effects of Levonorgestrel-Releasing Intrauterine Device(Mirena®) on Adenomyosis

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Objective: To evaluate the clinical effects of of levonorgestrel-releasing intrauterine device (Mirena®) on Adenomyosis.
Methods: From July, 2001 to August, 2004, 40 patients diagnosed as adenomyosis by ultrasonogram was participated in this study. Levonorgestrel-releasing intrauterine device (Mijna®) was inserted with patients with adenomyosis and the volume of uterus was measured 6 months later using transvaginal ultrasonogram. For 15 patients, the volume of uterus was measured after 12 months. The degree of dysmenorrhea was also evaluated at the time of intrauterine device insertion using visual analogue scale. 8 patients with adenomyosis participated as control group. Changes of uterine volume and pain score were measured during follow-up period. Differences in serum CA-125 level before and after the intrauterine device insertion was also evaluated.
Results: The mean age of the patients was 44 years old and mean parity was 1.75. Mean follow up months was 15 months. The mean uterine volume of adenomyosis patient was decreased to 148.35±54.78cc in 6 months after Mirena® insertion with statistically significance. The mean pain score was also significantly decreased to 7.4± 1.5 to 1.7± 0.9. The serum CA-125 level was elevated with mean value of 52.79±19.86 U/ml and was decreased to 27.39±19.11U/ml with statistically significance. One year follow-up group was statistically analyzed with ANOVA and the volume was significantly decreased after 12 months of Mirena® insertion. The mean uterine volume for the control group was 143.78cc and was increased to 161.94cc after mean follow up months of 10 months but was not statistically significant. The pain score was also slightly increased from 7.0±1.5 to 7.3±1.4, but was statistically insignificant.
Conclusion: For adenomyosis patients, the levonorgestrel-releasing intrauterine device (Mirena®) effectively decreases the volume of the uterus and symptomatically improves dysmenorrhea.

● *Key words* : **Levonorgestrel-releasing intrauterine device(Mirena®), adenomyosis, CA-125, uterine volume, pain score**

Adenomyosis remains an important cause of menorrhagia and dysmenorrhea, which can result in greats stress for the woman involved.[1] Traditionally, adenomyosis was diagnosed based on clinical findings and confirmed only after surgery. Until recently, hysterectomy has been advocated as the definitive treatment. However, non-invasive diagnosis is now possible using transvaginal ultrasonography and magnetic resonance imaging.[2] This had led gynecologists to seek for alternative treatments other than hysterectomy for the management of this frustrating disorder. Endometrial ablations,[3] danazol,[4] hormonal suppression with GnRH agonists[5] or levonorgestrel releasing intrauterine system have been introduced.[6,7] In this study, we evaluated the efficacy of a levonorgestrel releasing intrauterine system (Mirena®) in women with adenomyosis by changes in uterine volume, pain score and serum CA-125.

Materials and methods

From July, 2001 to August 2004, 48 women aged from 34 to 55 years old participated in this study with their informed consent. All patients had complaints of menorrhagia and dysmenorrhea for at least 6 months.

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Each woman underwent transvaginal ultrasonogram (TVS) examination with an Ultramark HDI 5000 unit (Advanced Technology Laboratories, Bothell, WA, USA) using a wide-band 5- to 9-MHz transducer. Diagnostic criteria by TVS, in accordance with previous studies,[8,9] were as follows: a globular and/or asymmetric uterus, a poorly defined focus of abnormal myometrial echotexture, distorted and heterogeneous myometrial echotexture, myometrial linear striations, and myometrial cysts. Globular and/or asymmetric uterus was defined as a regular enlarged uterus with possible myometrial asymmetry unrelated to leiomyoma. Heterogeneous myometrium was defined by the presence of an indistinctly defined myometrial area with decreased or increased echogenicity.[9] Myometrial hypoechoic linear striations were defined as a radiate pattern of thin acoustic shadowing not arising from echogenic foci and/or leiomyoma. Myometrial cyst was defined as a round anechoic area of 1 to 7 mm diameter.[8,9] With the exception of diffuse heterogeneous myometrium that appeared non-specific for adenomyosis, the diagnosis was made when at least one of the above criteria was met. Once the diagnosis was made, the volume of the uterus was measured. The uterine length was first measured from fundus to internal os with the vaginal probe in a sagittal plane. The probe was then turned through 90 degrees to a transverse plane and adjusted to give the maximum anteroposterior diameter. The anteroposterior and transverse diameters were then measured. The uterine volume was then calculated with use of the formula for a prolate ellipsoid (Volume = 0.52×Length×Anteroposterior diameter×Transverse diameter).

The degree of dysmenorrhea was evaluated using visual analogue scale, a 10 cm-linear analogue scale marked from 0 to 10 in which 0 represented no pain at all, and 10 represented the most severe pain.[11] The score was recorded by marking a point somewhere along the 10 cm line. At the same time, blood samples were taken to determine serum CA-125 level.

A levenorgestrel- releasing intrauterine device (Mirena , Schering, UK) was inserted in 40 patients. 8 patients participated as control group. All patients, including patients in control group underwent clinical and transvaginal ultrasonogram after 6 months for uterus volume measurement, pain score and serum CA-125. 12 months follow up uterine volume measurements with transvaginal sonogram was performed in 15 patients.

Statistical analysis was done by using the SPSS 10.0 package (SPSS Inc, Chicago, Il.). The comparisons were made using paired sample t-test and analysis of variance (ANOVA). P values <0.05 were considered to be statistically significant.

Results

Insertion of intrauterine device (Mirena®) was performed in all cases without anesthesia and without particular patient discomfort. The demographic factors including mean age, mean parity and mean follow up months are summarized in (Table 1.)

Initial volume of the uterus with Mirena® insertion group was 174.69±59.04cc, which was decreased to 148.35 54.78cc after 6 momths with statistically significance. Meanwhile, the volume of the uterus in control group increased from 143.78±37.90 cc to 161.94 ±51.30cc but was not statistically significant. In Mirena® insertion group, both the pain score and serum CA-125 levels were decreased with statistically significance. (Table 2)

The pain score decreased from 7.4±1.5 to 1.7±0.9, and serum CA-125 level decreased from 52.79±19.86 U/ml to 27.39±19.11U/ml. In control group, the pain score and serum CA-125 level increased slightly, from 7.0±1.5 to 7.3±1.4 and from 44.50±40.27 U/ml to 46.04±46.34 U/ml but were statistically insignificant.

12 months follow-up uterine volume measurement was performed in 15 patients. This group was statistically analyzed with ANOVA and the volume was significantly decreased after 12 months of Mirena® insertion. The initial mean volume of these patients was 207.39±65.58cc. The volume decreased to 173.19cc±63.59cc in 6 months and to146.23±42.98cc in 12 months. (Fig 1)

Table 1. Demographic factors

	Mirena® Insertion Group	Control Group
Total patients number	40	8
Mean age	44	46
Mean parity	1.75	1.4
Mean follow-up months	15.0	12.9

Table 2. Clinical effects of Mirena®

Initial	174.69±59.04	52.79±19.86	7.4±1.5
6 months after Mirena® Insertion	148.35±54.78*	27.39±19.11*	1.7±0.9*
Control	143.78±37.90	44.50±40.27	7.0±1.5
Control Follow-up	161.94±51.30	46.04±46.34	7.3±1.4

* p <0.05 for the significant change after Mirena® Insertion (paired t-test)

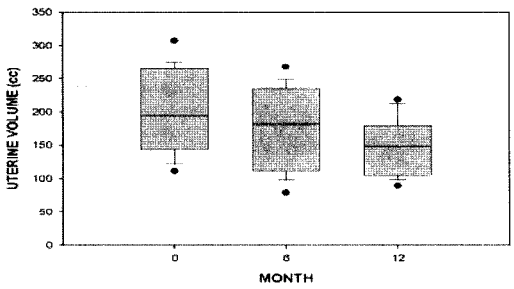

Fig. 1. Change of Uterus volume in 6 months and 12 months after Mirena® insertion

Discussion

The levonorgestrel-releasing intrauterine diveice (Mirena®, Schering, UK) is a highly effective contraceptive,[12] and recent studies emphasize its non-contraceptive benefits, especially in treating menorrhagia.[13,14] Randomized trials have confirmed its superior efficacy when compared with conventional medical treatment for menorrhagia 15 and its comparability with hysteroscopic surgical ablation of the endometrium.[16]

Our study indicates that a levonorgestrel releasing intrauterine device (Mirena®) is very effective in reducing uterine size associated with adenomyosis, as well as in reducing adenomyosis-associated dys menorrhea. The uterus volume decreased from mean volume of 174.69±59.04cc to 148.35±54.78cc after 6 months significantly, with mean 16% reduction of uterus volume. The largest volume reduction was noted in the patient with the initial uterus volume of 199.84cc. 44.6% volume reduction occurred after 6 months of Mirena® insertion. The volume decreased in 12 months follow-up group with statistically significance as well. The volume decreased from 207.39±65.58cc to 146.23±42.98cc in 12 months representing mean 29.5% decrease in size of the uterus. The volume was decreased continuously and consistently, showing 16.6% reduction in the first 6 months, and 15.6% reduction in the latter 6 month. This result is similar with other study.[5,7] However, the volume reduction was much greater in our study. In the previous study, the limited reduction in size may result from the selection of cases, which could have excluded women with grossly enlarged uterus. The efficacy of a levonorgestrel in adenomyosis may be attributed to two different actions of this device. First,

it causes decidualization and subsequent marked atrophy of endometrium.[6] This probably accounts for the marked reduction in menstrual flow. Secondly, there is also a direct action of hormone on the foci of adenomyosis. Mirena® has been shown to cause down-regulation of estrogen receptors in both glandular and stromal endometrial tissues and may prevent further stimulation by estrogen, leading to atrophy and shrinkage of adenomyosis foci.[17]

Our study provides evidence that Mirena® is effective in the controlling the pain associated with adenomyosis. The effect of levonorgestrel-releasing intrauterine device on pelvic pain has been well documented in several studies with endometriosis.[18-20] In previous study by Lockhat et al. a 10 cm visual analogue scale (VAS) dysmenorrhea score of endomteriosis patients fell from a pre-insertion value of 7.7±1.3 to 2.7±1.5 at 36 months and the most dramatic improvement in symptoms occurred during the first 12 months of therapy.[20] Our results were very similar, with pain score dropping from a pre-insertion value of 7.4±1.5 to 1.7±0.9. However, the dramatic improvement was noticed in shorter period of time. Patients showed improvement of symptoms starting from the first month of insertion, and within 6 months, most patients were relieved from dysmenorrhea. Although it was not mentioned in results, in 12 months follow-up group, there were no significant changes of symptoms over the remaining 6 months. How Mirena® improves pelvic pain and dysmenorrhea caused by endometriosis has not been fully understood, yet. These results are probably due to the amenorrhea or hypomenorrhea associated with endometrial atrophy induced in most women by the locally released levonorgestrel. A receptor mediated effect at the level of the endometriotic foci has been suggested. Another possible mechanism is by decreasing the vascular supply to the pelvis with relief from pelvic congestion. To determine the effect of the levonorgestrel-releasing IUD on the impedance to blood flow in the uterine arteries, the evaluation of transvaginal color Doppler ultrasonography in patients with adenomyosis before and after IUD insertion is currently on the way.

In this study, we evaluated the correlation between adenomyosis and serum CA-125 level. Serum CA-125, a 200,000 Da glycoprotein, concentration has been associated with the presence of many gynecologic disorders including malignant ovarian tumors, cervical and endometrial cancer, endometriosis, leiomyoma, ectopic pregnancy and adenomyosis.[21] The most important clinical use of this serum marker has been in monitoring the course of ovarian cancer in response to treatment. Recently, CA-125 is used as one of the principal serum markers in the diagnosis and management of late-stage endometriosis, but the assessment of CA-125 is of limited value in detecting women with minimal or mild disease. The value of serum CA-125 and the cut-off value in the diagnosis of adenomyosis has not been well established, yet. Zhou and associates investigated the value of CA-125 assays in the diagnosis of adenomyosis and found that CA-125 levels were positively correlated with uterine size in patients with adenomyosis and that the mean CA-125 level decreased significantly after the surgery.[22] In this study, increased serum CA-125 levels dropped significantly, from 52.79±19.86 U/ml to 27.39 ±19.11U/ml, 6 months after Mirena®, where as in control group, the level slightly increased from 44.50± 40.27 U/ml to 46.04±46.34 U/ml. It can be assumed that serial serum CA-125 may be useful in management and evaluating the success of a treatment in adenomyosis. To fully understand the clinical value of serum CA-125 in adenomyosis, further research with longer follow-up period is necessary.

After Mirena® insertion, most common complaint was vaginal spotting. 32 patients complained of irregular vaginal spotting in the first 3 months. Breakthrough bleeding in the most common adverse effect of Mirena® and remains the most important reason for discontinuation of use. However, none of the patients requested removal of the intrauterine device due to this complication. Spotting decreased progressively in subsequent months and subsided in most patients by 6 months.

Patients with adenomyosis often suffer from heavy bleeding and dysmenorrhea and these symptoms can be very stressful in many women. The primary aim of management should be to improve quality of life. Although many conservative and radical surgical

options are available for treatment of adenomyosis, this study suggests that Mirena® is very effective in treatment for adenomyosis and can be considered as the first line treatment for adenomyosis.

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= 국문 초록 =

연구목적: 본 연구는 Levonorgestrel 함유 자궁내 장치(Mirena®)가 자궁선근증 환자에 미치는 치료 효과와 영향에 대해 알아보고자 하였다.

연구방법: 2001년 7월부터 2004년 7월까지 Levonorgestrel 함유 자궁내 장치(Mirena®)를 삽입한 자궁선근증 환자 48명을 대상으로 시행하였다. 질식 초음파로 자궁선근증을 진단한 환자에 대해 Levonorgestrel 함유 자궁내 장치(Mirena®)를 삽입하고 삽입당시의 질식 초음파를 이용하여 자궁 전체 용적을 측정하고 visual analogue scale을 이용하여 생리통에 대한 평가를 시행하였고 혈청 CA-125 수치를 측정하였다. 6개월 후 자궁 전체 용적, 혈청 CA-125 수치 및 통증에 대한 변화를 평가하였다. 15명의 환자에서는 12개월 후 자궁 전체 용적 변화를 측정하였고 8명의 환자가 대조군으로 본 연구에 참여하였다.

연구결과: 자궁선근증 환자의 평균 추적 관찰 기간은 15개월이었으며 평균 연령은 44세였다. 자궁 선근증 환자의 평균 자궁 용적은 174.69±59.04cc였으며 Levonorgestrel 함유 자궁내 장치(Mirena®) 삽입 6개월 후 자궁 용적이 148.35±54.78cc로 통계학적으로 의미 있게 감소하였다. 생리 통증 및 혈청 CA-125 수치 역시 Levonorgestrel 함유 자궁내 장치(Mirena®) 삽입 후 의미 있는 감소를 보였다. 12개월 추적 관찰 군에서도 역시 자궁 전체 용적이 의미 있는 감소를 보였다.

연구결론: Levonorgestrel 함유 자궁내 장치(Mirena®)는 자궁 선근증 환자에 있어서 자궁 용적의 감소를 유발시키고 생리통증을 감소시키며 혈청 CA-125 수치를 감소시키는 효과가 있다.

●중심단어: Levonorgestrel 함유 자궁내 장치(Mirena®), 자궁선근증