CLINICAL STUDY

Efficacy of Levonorgestrel Releasing Intrauterine System in Menorrhagia: A One-Year Follow-up Study

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Abstract

Objective: To assess the efficacy of the levonorgestrel intrauterine system in the treatment of menorrhagia.
Materials and Methods: Forty-eight premenopausal women, attending to our gynecology clinic with the complaint of menorrhagia were enrolled into the study. Clinical assessment tools of menstrual bleeding such as endometrial thickness, hemoglobin and serum ferritin levels were measured both before (Group A) and one year (Group B) after the insertion of the intrauterine device. Paired samples t test was used for comparing the differences between groups.
Results: At the end of the first year, 33 women (68.75%) were reached and the continuation rate was 75.75%. While the mean number of pads used daily during menstruation in Group B patients decreased, the hemoglobin and serum ferritin levels increased significantly. Hemoglobin levels increased from a mean value of 10.71±1.97 to 13.31±1.34 g/dl (P<0.001); serum ferritin levels increased from 15.77±16.20 to 34.53±30.62 ng/mL (P=0.001).
Conclusion: Levonorgestrel intrauterine system is an effective means of reducing blood loss in menorrhagia. It may be a good alternative for surgical treatment in menorrhagia.

Keywords: levonorgestrel, contraceptive device, intrauterine, menorrhagia, erythrocyte indices, ferritin

Özet

Menorajide Levonorgestrelli İntrauterin Sistemin Etkinliği: Bir Yıllık Sonuçlarımız

Amaç: Levonorgestrelli intrauterin sistemin menoraji tedavisinde etkinliğini araştırmak.
Materyal ve Metot: Menoraji yakınmasıyla Jinekoloji kliniğimize başvuran 48 premenopozal olgu çalışmaya dahil edildi. Menstrüel kanama miktarının klinik değerlendirilmesinde kullanılan parametrelerden olan endometriyal kalınlık, hemoglobin ve serum ferritin seviyeleri hem uygulamadan önce (Grup A) hem de intrauterin araç uygulandıktan bir yıl sonra (Grup B) ölçüldü. Gruplar arasındaki farkın karşılaştırılmasında paired samples t test kullanıldı.
Sonuçlar: Birinci yılın sonunda 33 hastaya (%68.75) ulaşılabildi ve tedaviye devam oranı %75.75 idi. Grup B hastalarda menstrüasyon döneminde kullanılan ortalama günlük ped sayısı azalırken, hemoglobin ve serum ferritin seviyelerinde anlamlı artışlar saptandı. Hemoglobin ortalama değeri 10.71±1.97 g/dl'den 13.31±1.34 g/dl'ye (P<0.001); serum ferritini 15.77±16.20 ng/ml'den 34.53±30.62 ng/ml'ye yükseldi (P=0.001).
Tartışma: Levonorgestrelli intrauterin sistem menorajide kan kaybını azaltmada etkilidir. Menoraji tedavisinde, cerrahi girişimin iyi bir alternatifi olabilir.

Anahtar sözcükler: levonorgestrel, intrauterin araç, kontraseptif, menoraji, eritrosit indeksleri, ferritin

Introduction

Menorrhagia is an important gynecologic problem in women's life. It accounts for more than 10% of outpatient referrals to gynecology consultants, and about half of the referred women will undergo hysterectomy within five years (1). Although hysterectomy is the definitive treatment modality, the associated morbidity and complication rates can not be ignored (2). Additionally, 80% of women treated for menorrhagia have no anatomical pathologies and over one third of the women undergoing hysterectomies for menorrhagia have anatomically normal uteri (3). Hence, medical therapy is an attractive alternative with avoidance of surgery. Commonly used medical therapies are the combined contraceptive pills,

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cyclical hormone replacements, non-steroidal anti-inflammatory drugs and tranexamic acid. Luukkainen (4) claimed that levonorgestrel releasing intrauterine system (LNG-IUS, Mirena®) was the most effective pharmacological treatment of menorrhagia and, because it was effective for more than 5 years, it was also the most cost-effective.

The LNG-IUS was first introduced in 1986. It is a hormonally medicated intrauterine device which releases its synthetic progestin into the endometrial cavity at a rate of 20 µg/day over a 5-year period. Though it was developed primarily as a contraceptive device, also licensed for the management of menorrhagia (5).

We undertook this prospective trial to evaluate the efficacy of the LNG-IUS in the long-term treatment of the menorrhagia.

Materials and Methods

Premenopausal women attending to our gynecology clinic with the complaint of menorrhagia were recruited the study. Approval was obtained from the medical ethical committee of our hospital and informed consents were taken.

Subjects with known or suspected pregnancy, history of pelvic inflammatory disease, thromboembolism, malignancy, cardiac and hepatic disease, severe depression, uterine malformation, use of any contraceptive pills and oral progestins during previous 3 months were excluded. Fibroids less than ≤5 cm detected by ultrasonography were acceptable. Following a thorough history and gynecologic examination, we combined the following methods to rule out the structural or intracavitary lesions; transvaginal sonography (TVUS), saline infusion sonography and endometrial curettage. Endometrial curettage was performed in an outpatient setting and all the endometrial curettages were benign in nature.

According to the inclusion and exclusion criteria, a total of 48 women were enrolled into the study initially. All the TVUS examinations were performed by 6-7.5 MHz vaginal probes (Aloka SSD 5500) by the same examiner. Endometrial thickness was measured as the thickest part in longitudinal section, including both endometrial layers.

Although menorrhagia is clinically defined as greater than or equal to 80 mL blood loss per menstrual cycle, it is the women's perception of her own menstrual loss which is the key determinant in her referral. Considering this fact, as clinical measures of menstrual bleeding, numbers of pads used per day during menstruation were noted. Serum ferritin concentrations and hemoglobin levels were measured by Enzyme Immuno-Assay and the cyanmethemoglobin detection method (with computerized fully automated hematology analyzer; Symex SE-9000), respectively.

Serum hemoglobin and ferritin concentrations were measured before insertion (Group A). LNG-IUS was inserted into the uterine cavity after menstruation according to the insertion instructions. The study was longitudinal with each subject acting as her own control. Clinical measures of menstrual bleeding, serum ferritin and hemoglobin levels were compared for statistical significance one year later (Group B). In Group B, the endometrial measurements were performed at the side of the vertical arms to avoid from the acoustic shadowing of the devices.

Statistical analysis was performed by using SPSS 10.0 for Windows (SPSS Inc., Chicago, IL. USA) statistical software. Descriptive statistics were shown as arithmetic mean±standard deviation. After the tests of normality, we used paired samples t test to investigate the differences between two groups. P value less than or equal to 0.05 was considered as statistically significant.

Results

Forty-eight women were enrolled into the study initially but thirty-three women (68.75%) were eligible for control at the end of the first year, others were lost to follow-up (Figure 1). Seventeen women were treated with oral progestins and two were with oral contraceptives prior to the insertion of the LNG-IUS but either discontinuation due to systemic side effects or poor patient compliance, the treatments were changed to LNG-IUS three months later. There were no complications experienced during insertion.

Mean age and duration of menorrhagia of the patients was 44.34±7.59 years and 17.58±26.45 months, respectively. Mean body mass index was 27.41±3.81 (range; 20.03-36.11). Pelvic examination revealed a slightly enlarged or normal uterus in most cases. Six women underwent hysterectomy; one for pelvic relaxation and others for unsuccessful treatment. LNG-IUS extractions were performed in three cases due to menopause in Group B. The devices were spontaneously expelled in three women after insertion; one underwent hysterectomy. In 15 cases, small fibroids less than 2 cm, in one case, 5 cm and in another 4 cm, as maximum diameters, were detected before insertion via TVUS but they showed no changes in size at a one-year follow-up.

The continuation rate was 75.75%. Nine patients were amenorrheic in Group B. There was significant decrease in mean number of pads used daily during menstruation in Group B whilst there were significant increases of mean hemoglobin and serum ferritin. Hemoglobin increased from a mean value of 10.71±1.97 to 13.31±1.34 g/dl (P<0.001); serum ferritin levels increased from 15.77±16.20 to 34.53±30.62 ng/mL (P=0.001).

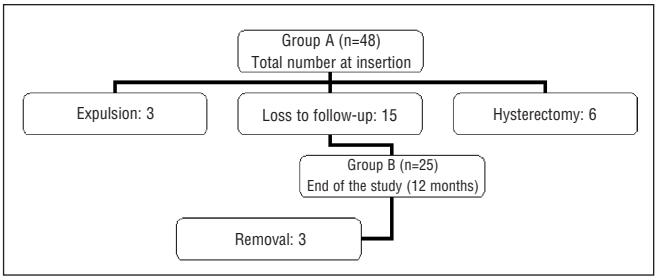

Figure 1. The profile of the trial.

Tablo 1. Clinical characteristics of the patients

Characteristic	Group A	Group B	*P* value
Duration of menstruation (day)	9.77±5.86	5.87±7.27	0.017*
Number of pads used daily	6.39±3.78	1.31±0.70	0.001*
Endometrial thickness (mm)	6.73±3.59	4.36±1.61	0.045*
Mean hemoglobin concentration (g/dl)	10.71±1.97	13.31±1.34	<0.001*
Mean serum ferritin (ng/ml)	15.77±16.20	34.53±30.62	0.001*
* Statistically significant			

Clinical characteristics of the patients are shown in Table 1.

Discussion

A woman's lifetime risk of hysterectomy is estimated as 20%. The high frequency of the operation and its complications lead to reevaluate medical treatment and to explore new conservative and surgical treatments for menorrhagia (6). To date, the LNG-IUS is one of the most effective reversible long-term treatments for menorrhagia (7). It was more effective than cyclical norethisterone taken for 21 days (3). Recently, the effectiveness of LNG-IUS was demonstrated to be comparable to operative treatments of menorrhagia (2,8). Although endometrial ablation is said to be a minimally invasive method compared to hysterectomy, it can be associated with complications such as perforation of the uterus (9).

The potential advantage of the LNG-IUS is its ease of use, its low cost and low complication rate. The use of LNG-IUS decreases the amount of menstrual blood loss (10). One year after insertion, most women bleed only for one day, and 15% became amenorrhoeic (11). The clinical performance of the LNG-IUS in our study was consistent with previous studies, confirming that the device is associated with significant reduction of menstrual bleeding. Faundes et al. (12) reported a prospective study in a population having a high incidence of anemia. They observed improvements both in body iron stores and hemoglobin concentrations in women using the LNG-IUS. We also observed very significant increases both in hemoglobin and serum ferritin levels.

Recently, Stewart et al. (13) reviewed the literature on the effectiveness of the LNG-IUS in menorrhagia and stated that hemoglobin levels had been reported in eight studies, serum ferritin in six studies. Among these studies, two of them had found no significant differences from baseline in hemoglobin and ferritin levels but six studies had reported improvements in hemoglobin and four studies in ferritin levels ranging 8-19.2% and 14.5-259%, respectively.

There are also studies in the literature investigating the efficacy of LNG-IUS in uterine leiomyomas and adenomyosis related menorrhagia (14-16). Grigorieva et al. (15) stated that hemoglobin concentrations increased significantly as early as 3 months after insertion, and changes in serum ferritin concentration became significant after 6 months in patients with menorrhagia due to leiomyomas. Also, the role of LNG-IUS in the treatment of endometrial hyperplasia had been investigated (17). The potential use of the device in this disease aroused from the knowledge that the localized delivery of LNG to the uterine cavity and endometrium achieved endometrial levels 200 times higher than in women receiving oral LNG (18).

The mechanisms responsible for reduced menstrual blood loss in LNG-IUS users are likely to be multifactorial and mostly due to the local progestative effect. Intrauterine release of LNG suppresses the endometrium (4). This results in endometrial atrophy and decidualization of the stroma as early as three months after insertion with a decrease of menstrual flow and decrease in number of bleeding days, leading to amenorrhea. A significant reduction in endometrial thickness one year later after insertion in our study might probably due to this effect. Silverberg et al. (19) demonstrated that the endometrium sampled 1 to 3 months after LNG-IUS removal after 5 years of use was completely normal, and no signs of previous IUS use had been detected. They concluded that the long term residence of LNG-IUS in the uterine cavity did not produce harmful effects on the endometrium.

There are also several advantages of the LNG-IUS in women with menorrhagia. While insertion provides 5 years of local treatment, additionally a safe contraception is achieved. The LNG-IUS produces a very high local concentration in the endometrial tissues with low plasma concentrations, providing the device with an excellent side-effect profile.

In conclusion, none of the treatments for menorrhagia is superior to other since all the treatments have their own advantages and disadvantages. It seems that LNG-IUS is an effective means of reducing blood loss in menorrhagia in our study. It may be a good alternative before deciding operative techniques in the treatment of menorrhagia.

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