Özgün Araştırma Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

Evaluation of Intrauterine Devices With Levonorgestrel in Patients With Heavy Menstrual Bleeding According to the Palm-Coein Classification System

Ağır Menstrüel Kanamalı Olgularda Levonorgestrelli İntrauterin Araç Etkinliğinin Palm-Coein Sınıflama Sistemine Göre Değerlendirilmesi

Emre Erdem TAŞ[1,2], Hüseyin Levent KESKİN[2], Gülin Feykan YEĞİN[2], Ayse Filiz AVŞAR[2,3]

[1] Antalya Education and Research Hospital, Department of Gynecology and Obstetrics Antalya, Turkey

[2] Atatürk Education and Research Hospital, Department of Gynecology and Obstetrics, Ankara, Turkey

[3] Yıldırım Beyazıt University, Department of Gynecology and Obstetrics, Ankara, Turkey

ABSTRACT

Aim: To evalute the efficacy of a levonorgestrel-releasing intrauterine device for the treatment of patients with heavy menstrual bleeding based on the PALM-COEIN (polyp; adenomyosis; leiomyoma; malignancy; hyperplasia-coagulopathy; ovulatory dysfunction; endometrial; iatrogenic; not yet classified) system.

Material and Methods: A retrospective study was performed of 110 cases that were grouped according to the PALM-COEIN classification system as those with or without structural abnormalities. For the 84 cases who completed 12 months of treatment, menstrual patterns, pictorial blood assessment chart (PBAC) scores, hemoglobin (Hb) values, and endometrial thickness changes were examined after 1,6 and 12 months. Independent sample t-tests,repeated-measures ANOVA, post-hoc Bonferroni adjustment and chi-squared tests were used for statistical evaluation.

Results: After 12 months of treatment, 73.8% of cases achieved a normal menstrual pattern. The PBAC score decreased by 80.6% in the COEIN group and 83.9% in the PALM group. The PBAC scores and endometrial thicknesses were decreased ($p<0.001$) and the Hb values were increased ($p<0.001$) after 12 months of treatment, with no intergroup differences ($p>0.05$). The PBAC score was higher in the PALM group compared to the COEIN group at 1 month, but this difference disappeared by 6 months of treatment ($p>0.05$).

Conclusion: The levonorgestrel-releasing intrauterine device has high levels of effectiveness in cases with or without structural uterine abnormalities.

Key Words: Levonorgestrel, intrauterine devices, menorrhagia, pictorial blood assessment chart, PALM-COEIN.

ÖZET

Amaç: Ağır menstruel kanamalı olguların tedavisinde levonorgestrel salgılayan intrauterin araç etkinliğinin PALM-COEİN (polip; adenomiyozis; leiomyoma; malignensi; koagülopati; endometrial hiperplazi; ovulatuar disfonksiyon; iatrojenik; henüz sınıflandırılmamış) sistemine göre etkinliğini belirlemek.

Gereç ve Yöntemler: Yapısal anomalisi bulunup bulunmamasına göre PALM-COEİN sınıflama sistemi ile gruplandırılan 110 olgu retrospektif olarak incelendi. Oniki aylık tedaviyi tamamlayan 84 olgunun menstruel paternleri, 'pictorial blood assessment chart (PBAC) skorları, hemoglobin (Hb) değerleri ve endometrial kalınlıklarındaki 1, 6 ve 12. aydaki değişikleri incelendi. İstatistiksel değerlendirmede Independent sample t-tests, repeated-measures ANOVA, post-hoc Bonferroni düzeltmesi ve ki-kare testleri kullanıldı.

Bulgular: Tedaviye başlangıçtan 12 ay sonra olguların % 73.8'i normal menstruel paterne kavuştu. PBAC skoru COEIN grubunda % 80.6, PALM grubunda ise % 83.9 azaldı. Tedaviye başladıktan 12 ay sonra her iki grupta PBAC skoru ve endometrial kalınlık azalırken ($p<0.001$), Hb değerleri artmıştı ($p<0.001$). Gruplar arasında ise farklılık yoktu ($p>0.05$). PBAC skoru tedavinin 1. ayında PALM grubunde COEİN grubuna göre daha yüksek olsa da, bu farklılık tedavinin 6. aynından itibaren kaybolmuştu ($p>0.05$).

Sonuç: Levonorgestrel salgılayan intrauterin araçlar yapısal uterin anomalisi olsun olmasın yüksek oranda etkinlik göstermektedir.

Anahtar Kelimeler: Levonorgestrel, intrauterin araç, menoraji, pictorial blood assessment chart, PALM-COEIN.

Yazışma Adresi/ Correspondence Address:
Emre Erdem Taş
Uluç Mahallesi, 1171 Sokak, Casa Viva Sitesi C Blok No:5 Konyaaltı \ Antalya, Türkiye
Tel /Phone :+90 506 603 57 77 E-mail: vote@mynet.com

Geliş Tarihi/ Received: 07.08.2014
Kabul Tarihi/ Accepted: 30.09.2014

Introduction

Menorrhagia/hypermenorrhea is classically defined by a volume during menstrual bleeding of ≥80 ml or a bleeding duration exceeding 7 days (1). An estimated 10–30% of women of reproductive age are affected (1). Excessive bleeding decreases the woman's quality of life (1,2) and can cause secondary diseases, such as anemia (3) and imposes a marked financial burden on healthcare systems (1). Menorrhagia can be treated by a range of surgical and medical treatments, including endometrial ablation, hysterectomy, tranexamic acid, oral contraceptives with estrogens and progestins or synthetic progestins only, and nonsteroidal anti-inflammatory drugs.

The levonorgestrel-releasing intrauterine device (LNG-IUD) is one of the most important recent advances in medical treatment options for menorrhagia (4). The Mirena® is a small, long-acting LNG-IUD that provides high levels of contraceptive reliability. In addition, the Mirena® can be an effective treatment for menorrhagia. Randomized controlled studies comparing the LNG-IUD with other therapies for excessive menstrual bleeding reported a greater decrease in menstrual bleeding and better patient compliance with the use of the LNG-IUD (5,6). Therefore, some authors have recommended its use as a "first-line therapy" for patients with excessive menstrual bleeding who wish to preserve their fertility (7). However, as with other menstrual disorders, assessments or comparisons of the treatment efficacy of the LNG-IUD in case groups with menorrhagia of different etiologies have been hampered by the lack of a universal terminology or classification system.

In 2011, the Menstrual Disorders Working Group of the International Federation of Gynecology and Obstetrics (FIGO) proposed a classification system and standardized terminology for etiologies of the symptoms of abnormal uterine bleeding (AUB). This system and terminology were approved by the FIGO executive board and supported by the American College of Obstetricians and Gynecologists (ACOG) (8,9). With this system, the term "heavy menstrual bleeding (HMB)" replaces the term "menorrhagia". Etiologies of AUB are classified as "related and unrelated to uterine structural abnormalities" and categorized according to the PALM-COEIN acronym: Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic and Not otherwise classified (8). The objective of this study was to evaluate the efficacy of the LNG-IUD in the treatment of HMB cases, on the basis of their etiological classification with the PALM-COEIN system.

Material and Methods

This study included 110 cases who underwent insertion of an LNG-IUD (Mirena®, Bayer Schering Pharma, Berlin, Germany) for the treatment of HMB between January 2010 and December 2011. The pictorial blood assessment chart (PBAC), which is an indirect method of measuring the amount of menstrual bleeding, was used in all cases. A PBAC score ≥ 100 was considered to indicate menorrhagia (10). Cases that received an LNG-IUD were assessed at 1, 6, and 12 months after IUD insertion in our clinic. Menstrual patterns, PBAC scores, hemoglobin (Hb) values, and endometrial thicknesses, as assessed by transvaginal ultrasound, were evaluated during follow-up visits.

After the introduction of the PALM-COEIN classification system, the medical records of 110 cases were assessed. Retrospectively evaluated data included the following: pretreatment histories; physical examination findings; laboratory values, including whole blood count, bleeding profiles, serum beta human chorionic gonadotropin, follicular stimulating hormone, luteinizing hormone, prolactin, thyroid stimulating hormone (TSH), triiodothyronine (fT3), free thyroxine (fT4), and mid-luteal serum progesterone, tested on the third day of menstruation; radiological imaging results, including ultrasonography, magnetic resonance imaging, and computerized tomography; and endometrial sampling results. Cases were classified according to the PALM-COEIN classification system. Thirty-five cases (31.8%) had leiomyomas, with an average size of 5.3 ± 2.9 cm (range, 2-16 cm); however, none of the leiomyomas had submucosal locations and there was no compression of the endometrial cavity. Except for the seven cases (6.4%) with cardiovascular or cardiac valvular diseases, and cases using anticoagulants, the bleeding profiles, thyroidal function tests (TSH, fT3, and fT4), and serum prolactin values were normal. The serum Hb value in 72 (65%) cases was <12 g/dl, which is accepted as the anemia limit in nonpregnant women of reproductive age. Oral iron therapy (80–100 mg iron II sulphate) was prescribed for 11 (10%) women with Hb values < 10 g/dl for at least 6 months (11).

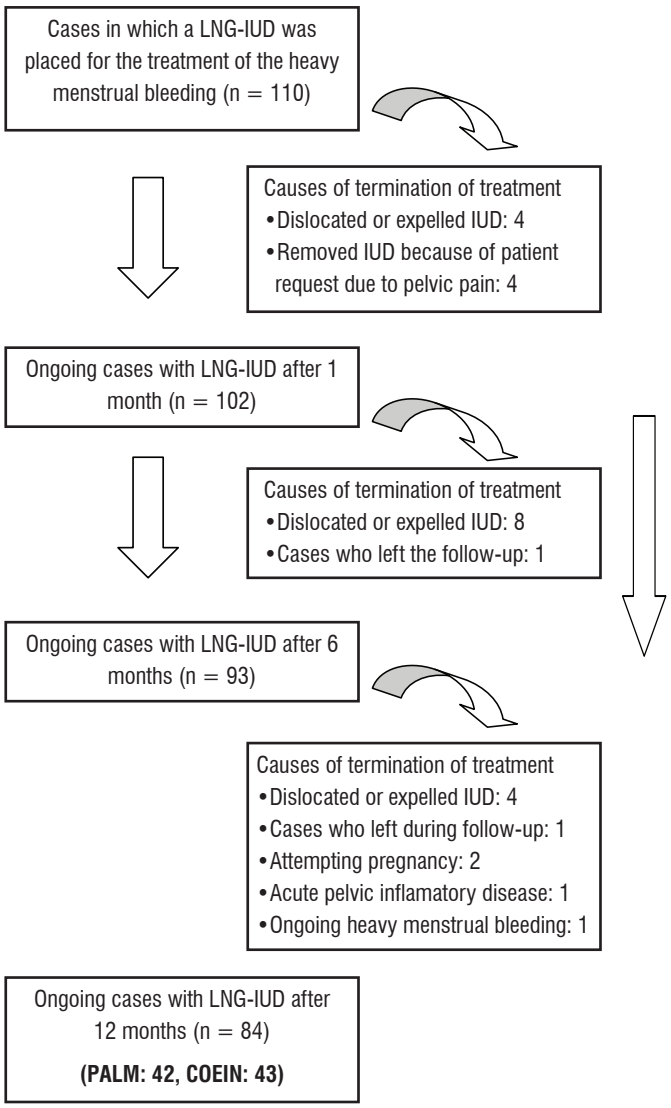
Endometrial samplings were reported as simple endometrial hyperplasia without atypia in 15 cases (13.6%), endometrial polyps in 7 cases (6.4%), and endometritis in 2 cases (1.8%). Forty-four (40%) cases had ovulatory dysfunction according to serum hormone, endometrial sampling, and ultrasonographic findings. There was no case of adenomyosis or systemic bleeding disorder.

When the features of the 110 cases were examined retrospectively, 57 cases (51.8%) were in the PALM group and 53 (48.2%) cases were in the COEIN group. The 12-month follow-up findings of the 110 cases were examined. Twenty-six cases were excluded from the study for several reasons (Figure 1). Except for 2 cases who left the study during the follow-up period, the device was removed or expelled in 16 of the remaining 24 excluded cases (66.6%) because of cervical dislocation or expulsion of device ($n = 9$ in the PALM group, $n = 7$ in the COEIN group, $p > 0.05$). Myomas were present in eight cases with expulsion/dislocation in the PALM group.

The medical records of the remaining 84 cases who completed the 12-month follow-up were examined. Their menstrual patterns, PBAC scores, Hb values, and endometrial thicknesses at 1, 6, and 12 months were evaluated.

Statistical analyses were performed with SPSS version 17 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to assess the data normality. Complementary statistical results were shown as the mean ± standard deviation (SD) for normally distributed data, and as the median (interquartile range, IQR) for nonparametric data. The results of the 84 cases with repeated measurements were performed, and the PALM and COEIN groups were compared with independent samples t-tests. Intragroup temporal changes of the data were examined by repeated-measures ANOVA. The post-hoc Bonferroni adjustment was applied to find the time intervals to which the temporal changes were related. Categorical variables were compared by the chi-squared test. A p-value of <0.05 was accepted as the limit of statistical significance in all tests, and $p < 0.0125$ (0.05/measurement intervals) was accepted as the limit of statistical significance after the Bonferroni adjustment test.

Figure 1: Flow chart of the study protocol



Results

For the 84 cases with repeated measurements, the average age was 41 ± 5.7 years (range, 23–49 years), and the median (IQR; range) gravidy and parity were 3 (3.0–16) and 3 (1; 0–11), respectively. The numbers of cases that described intermenstrual bleeding at the 1- and 6-month follow-up visits were 51 (60%) and 38 (45%), respectively, compared to 3 (3.5%) at the 12-month visit. Sixty-two cases (73.8%) achieved a normal menstrual pattern by 12 months. Ten cases developed amenorrhea that continued for at least 6 months. The PBAC scores and endometrial thicknesses decreased during the treatment period compared to the pretreatment values ($p < 0.001$, repeated measures ANOVA). The Hb values in the pretreatment period were not different from those after 1 month of treatment (11.3 vs. 11.4, $p = 0.062$), but they began to increase thereafter ($p < 0.001$). The PBAC scores decreased by 82.3% in all cases, by 80.6% in the COEIN group, and by 83.9% in the PALM group to the twelfth month.

Table 1 shows all of the results for the PBAC scores, endometrial thicknesses, and Hb values for the 84 patients before treatment and at each follow-up time point. The PBAC scores were higher in the PALM group than in the COEIN group before treatment and after the first month of IUD treatment ($p = 0.043$ and 0.037, respectively). This difference disappeared by 6 and 12 months ($p > 0.05$). The Hb levels and endometrial thicknesses did not differ among the groups at any time point after treatment ($p > 0.05$).In both groups, the PBAC score decreased throughout the treatment period ($p < 0.001$). In the COEIN group, the endometrial thickness after 1 month of treatment was similar to the pretreatment value ($p = 1.000$); however, the thickness decreased thereafter ($p < 0.001$). Endometrial thickness decreased in every follow-up interval throughout the treatment period ($p \leq 0.001$). In both groups, the Hb values were not different from the pretreatment values within 1 month of insertion ($p > 0.05$), but they began to increase thereafter ($p < 0.001$).

Table 1. Results for the PBAC scores, endometrial thicknesses and Hb values before treatment and at each follow-up time point

		Total subjects (n =84)	COEIN group (n =44)	PALM group (n =40)	
		Mean ± SD			p**
PBAC score	Pretreatment	345 ±147	315±141	379±147	0.043
	1st month	283 ±141	255±123	315±154	0.037
	6th month	103 ±38	101±44	106±30	0.348
	12th month	61 ±27	61±31	61 ±23	0.981
	p*	<0.001	<0.001	<.0.001	
Hgb (gr/dl)	Pretreatment	11.3 ±1.4	11.3±1.4	11.2±1.5	0.382
	1st month	11.4 ±1.4	11.4±1.3	11.4±1.4	0.417
	6th month	12.1 ±1.0	12.8±1.0	12.9±1.0	0.613
	12th month	12.9±1.0	12.8±1.0	12.9±1.0	0.656
	p*	<0.001	<0.001	<0.001	
ET (mm)	Pretreatment	9.9±4.4	9.0±4.3	10.7±4.3	0.241
	1st month	8.7±2.8	8.5±2.6	9.0±3.0	0.969
	6th month	6.5±2.0	6.2±1.6	6.7±2.3	0.398
	12th month	5.2±1.3	5.2±1.3	6.7±2.3	0.854
	p*	<0.001	<0.001	<0.001	

*p*Repeated measures values, p** between the groups*

ET: Endometrial thicknesses, PABC: The pictorial blood assessment chart, Hgb: Hemoglobin

Discussion

Randomized controlled studies of conservative treatment methods for HMB report high success rates with LNG-IUD therapy. However, it is difficult to predict the treatment efficacy in patient groups with different etiologies (5,7), due to the lack of a common terminology or etiology-based classification system (8,9). It is hoped that the new PALM-COEIN classification system will fill this gap (8,9). As an important advantage, more patients who are treated with an LNG-IUD continue with treatment compared to those who are treated with other medical methods (5). Studies that are methodologically similar to the current study and analyses of HMB cases treated with LNG-IUDs have shown that 59–98 % of cases had the IUD in situ for 12 months (after the cases that left the follow-up were excluded) (12-15). The rate of treatment continuation is lower in cases with structural uterine abnormalities, including leimyoma or adenomyosis (13,16).

Excluding the two cases who left the study during the follow-up period, 77% of our cases completed the 12-month follow-up period with the IUD in place, consistent with rates in the literature. The main reason for early termination of treatment was expulsion/dislocation of the device, which occurred in two-thirds of the terminated cases (14.8% of all cases). Although the expulsion/dislocation rate was higher in the group with structural uterine abnormalities, the difference was not statistically significant (9 vs. 7, $p > 0.05$). In similar studies, only the expulsion rate was calculated (0–13.36%), which was higher in cases with structural uterine abnormalities, such as leiomyoma (12-14,16,17). In our study, none of the cases terminated the treatment as a result of amenorrhea, intermenstrual bleeding, or other adverse effects.

The PBAC score in the PALM group was higher in the pretreatment period and after 1 month of treatment compared to the COEIN group; however, the difference between the groups disappeared after 6 months. In both groups, by 12 months, the PBAC scores were significantly lower than the pretreatment values. In methodologically similar studies, the decrease in PBAC scores at 12 months ranged from 69% to 98%; however, these studies lacked the etiological classification of the cases (12-17). In the present study, the PBAC score decreased by 82.3% in the entire cohort by the end of 12 months; this decrease was similar in both groups (80.6% in the COEIN group vs. 83.9 in the PALM group).

Amenorrhea developed in 12% of cases in 12th month. This finding is comparable to studies in the literature, in which the amenorrhea rate was reported to be 5–46% (12-17). The rate of cases that achieved a normal menstrual pattern was higher in our study than in similar previous studies (13,15,17). The effect of the LNG-IUD on menstruation is mainly due to its antiproliferative effect on the endometrium, which leads to endometrial suppression, decidualization, and atrophy, and a decrease in endometrial thickness (18). The endometrial thickness began to decrease after the first month of IUD treatment in the COEIN group. Decreases were observed in PALM group, including the endometrial hyperplasia subgroup, during the whole period of the treatment. Our findings support studies that have recommended the use of LNG-IUD for the treatment of endometrial hyperplasia (12,18).

An important advantage of LNG-IUD in cases with HMB is that it increases serum Hb levels. This effect is important in regions such as Turkey, where the prevalence of anemia is high among women of reproductive age (12,17,19). As shown in our study, LNG-IUD is an effective adjuvant therapy to increase the serum Hb levels in cases with and without structural uterine abnormalities. Its effects significantly increase with increasing duration of treatment (15,19).

In our study, although no cases were present under some acronyms of AUB, including A (proven adenomyosis), I (idiopathic) and N (not otherwise classified), similarly high levels of efficacy were found with the use of LNG-IUD in cases with structural uterine abnormalities (AUB – P, L, and M) and in cases with HMB related to nonstructural causes (C, O, and E).

The retrospective design is a limitation of the present study. Our outcomes must be confirmed by further prospective studies.

References

1. Liu Z, Doan QV, Blumenthal P, Dubois RW. A systematic review evaluating health-related quality of life, work impairment, and health-care costs and utilization in abnormal uterine bleeding. Value Health 2007;10:183-94.
2. Gokyildiz S, Aslan E, Beji NK, Mecdi M. The Effects of Menorrhagia on Women's Quality of Life: A Case-Control Study. ISRN Obstet Gynecol 2013;8:918179.
3. Palacios S. The management of iron deficiency in menometrorrhagia. Gynecol Endocrinol 2011;27:1126-30.
4. Marret H, Fauconnier A, Chabbert-Buffet N, Cravello L, Golfier F, Gondry J et al Clinical practice guidelines on menorrhagia: management of abnormal uterine bleeding before menopause. Eur J Obstet Gynecol Reprod Biol 2010;152:133-7.
5. Milsom I. The levonorgestrel-releasing intrauterine system as an alternative to hysterectomy in peri-menopausal women. Contraception 2007;75:152-4.
6. Lee BS, Ling X, Asif S, Kraemer P, Hanisch JU, Inki P. Levonorgestrel-releasing intrauterine system versus conventional medical therapy for heavy menstrual bleedingin the Asia-Pacific region. Int J Obstet Gynecol 2013;121:24-30.
7. Hurskainen R, Paavonen J. Levonorgestrel-releasing intrauterine system in the treatment of heavy menstrual bleeding. Curr Opin Obstet Gynecol 2004;16:487-90.
8. Munro MG, Critchley HO, Broder MS, Fraser IS; FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nongravid women of reproductive age. Int J Gynaecol Obstet 2011;11:3-13.
9. Committee on Practice Bulletins—Gynecology.Practice bulletin no. 128: diagnosis of abnormal uterine bleeding in reproductive-aged women. Obstet Gynecol 2012;120:197-206.
10. Higham JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. Br J Obstet Gynecol 1990;97:734-9.
11. McLean E, Cogswell M, Egli I, Wojdyla D, de Benoist B. Worldwide prevalence of anaemia, WHO Vitamin and Mineral Nutrition Information System, 1993-2005. Public Health Nutr 2009;12:444-54.

12. Kriplani A, Singh BM, Lal S, Agarwal N. Efficacy, acceptability and side effects of the levonorgestrel intrauterine system for menorrhagia. Int J Gynaecol Obstet 2007;97:190-4.

13. Mercorio F, De Simone R, Di Spiezio Sardo A, Cerrota G, Bifulco G, Vanacore F, Nappi C. The effect of a levonorgestrel-releasing intrauterine device in the treatment of myoma-related menorrhagia. Contraception 2003;67:277-80.

14. Kriplani A, Awasthi D, Kulshrestha V, Agarwal N. Efficacy of the levonorgestrel-releasing intrauterine system in uterine leiomyoma. Int J Gynaecol Obstet 2012;116:35-8.

15. Chattopdhyay B, Nigam A, Goswami S, Chakravarty PS. Clinical outcome of levonorgestrel intra-uterine system in idiopathic menorrhagia. Eur Rev Med Pharmacol Sci 2011;15:764-8.

16. Peng FS, Wu MY, Yang JH, Chen SU, Ho HN, Yang YS. Insertion of the Mirena intrauterine system for treatment of adenomyosis-associated menorrhagia: a novel method. Taiwan J Obstet Gynecol 2010;49:160-4.

17. Desai RM. Efficacy of levonorgestrel releasing intrauterine system for the treatment of menorrhagia due to benign uterine lesions in perimenopausal women. J Midlife Health 2012;3:20-3.

18. Varma R, Soneja H, Bhatia K, Ganesan R, Rollason T, Clark TJ, Gupta JK. The effectiveness of a levonorgestrel-releasing intrauterine system (LNG-IUS) in the treatment of endometrial hyperplasia--a long-term follow-up study. Eur J Obstet Gynecol Reprod Biol 2008;139:169-75.

19. Xiao B, Wu SC, Chong J, Zeng T, Han LH, Luukkainen T. Therapeutic effects of the levonorgestrel-releasing intrauterine system in the treatment of idiopathic menorrhagia. Fertil Steril 2003;79:963-9.