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"ORMELOXIFENE AND MEDROXYPROGESTERONE IN ABNORMAL UTERINE BLEEDING" – A COMPARATIVE STUDY

Obstetrics & Gynaecology

K Jaya Sathya Post Graduate, Department of Obstetrics And Gynaecology: Santhiram Medical College, Nandyal, India.

I Siva Jyothi Associate Professor, Department of Obstetrics And Gynaecology: Santhiram Medical College, Nandyal, India.

ABSTRACT

BACKGROUND: The purpose of this study was to compare the effects of ormeloxifene with medroxyprogesterone acetate in patients with abnormal uterine bleeding **MATERIALS AND METHODS:** 100 Patients were divided into two groups. In group A, ormeloxifene was given at the dosage of 60 mg twice a week for 3 months followed by 60 mg once a week for 1 month. In group B, medroxyprogesterone acetate was given at the dosage of 10 mg twice a day from day 5 to day 25 of the menstrual cycle. At followups, patients were assessed for PBAC score, endometrial thickness by USG, hemoglobin level, and the side effects of drug therapy. **RESULTS:** There were 54 patients in group A and 46 in group B. Reduction in median PBAC score was 79.4 % in group A and 75 % in group B after 4 months of treatment. The mean duration of bleeding reduced to 4.8 from 9 in group A and 5 from 8.7 in group B. Mean hemoglobin was increased from 8.6 to 9.8 g % in group A and from 8.7 to 9.9 g % in group B; endometrial thickness was reducedfrom 7.7 mm to 6.8 mm in group A and from 7.4 mm to 6.9 mm in group B.**CONCLUSION:** We conclude from this study that ormeloxifene should be considered the first choice in the management of AUB, especially in the perimenopausal age group where amenorrhea is acceptable.

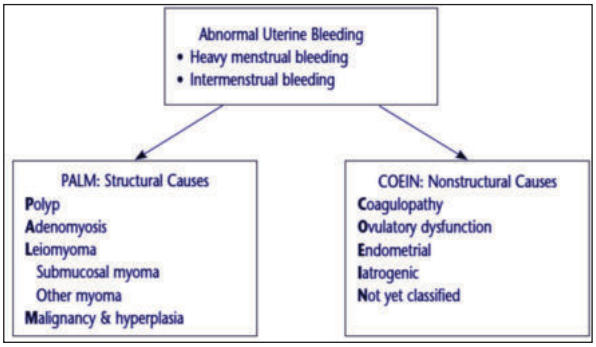
KEYWORDS

Abnormal uterine bleeding _ Ormeloxifene _Medroxyprogesterone _ PBAC score _ DUB

INTRODUCTION

Abnormal uterine bleeding (AUB) is defined as bleeding from uterine corpus which is abnormal in regularity, volume, frequency, and duration of bleeding, and it occurs in the absence of pregnancy [1]. It can be acute and chronic. It is one of the major gynecological problems affecting women wellbeing for which women seek health personnel. In a national study of the United States, the authors found that menstrual disorders were the reason for 19.1 percent of 20.1 million visits to doctors clinics for gynecological conditions over a two-year period [2]. Any patient with AUB should be evaluated regarding her clinical status and severity, etiology, and the most appropriate treatment. The new classification (Table 1) system of etiology of AUB has been proposed by the Menstrual Disorders Working Group of the International Federation of Gynecology and Obstetrics [1]. Surgical treatment is often needed for all structural causes, while for the nonstructural causes, medical treatment should be the first choice. The choice of treatment depends on the cause, age, severity of bleeding, fertility status, need for contraception, and the treatment available at the center. Among the medical category, there are various options as combined oral contraceptives, progestins (oral or intramuscular), levonorgestrel intrauterine device, antifibrinolytics such as tranexemic acid and danazol, gonadotropins releasing hormone, etc., but every treatment option has its own benefits and risks, and in some cases cost is also an issue. In the literature, still there is no gold standard treatment for AUB. Ormeloxifene is a newer non-steroidal alternative for the treatment of AUB. However, there are limited number of studies available on its efficacy and safety. It is also known as centchroman, a nonsteroidal, selective estrogen receptor modulator (SERM), with potent estrogen antagonistic action on uterus as well as breast tissue and mild agonistic action on bone mineral density [3, 4]. It is very effective, reducing up to 70 % blood loss with minimal side effects, has an easy dosing schedule, and cost efficient [5].

Table 1 PALM-COEIN classification system for etiology of abnormal uterine bleeding in nonpregnant reproductive aged women



MATERIALS AND METHODS

A prospective, Analytical and Comparative study done in Santhiram Medical College . From period of Febrauary 2021-July2021

INCLUSION CRITERIA:

Patients with AUB aged between 20-50 years are included,who are willing to participate and to give written informed consent.

EXCLUSION CRITERIA:

1. Patients with leiomyoma, adenomyosis,polyp,adnexal masses, systemic disorders ,coagulopathy,breast malignancy, endometrial hyperplasia with atypia are excluded.
2. Patients who are not willing to participate and not willing to give written informed consent are excluded

Patients were divided into two groups. In group A, ormeloxifene was given at the dosage of 60 mg twice a week for 3 months followed by 60 mg once a week for 1 month. In group B, medroxyprogesterone acetate (MPA) was given at the dosage of 10 mg twice a day from day 5 to day 25 of the menstrual cycle. After detailed history and clinical examination, every patient was subjected to the assessment of Pictorial blood loss assessment chart (PBAC) scoring, hemoglobin level, endometrial thickness on ultrasonography, and endometrial biopsy and Pap smear. Follow-up was done at 2nd and 4th month, and again at each follow-up their clinical characteristics of bleeding, PBAC score, hemoglobin level, and endometrial thickness were assessed and the side effects of therapy, if any, were also noted. Pictorial blood loss assessment chart (PBAC) is used to measure the amount of menstrual blood loss [6]. In this method, women are asked to use certain sanitary napkins which have similar absorbent capacities. They record the number of napkins used in a cycle. Number and size of clots passed are also noted. Scores are assigned to different degrees of soiling of sanitary napkins and number and size of clots passed. Scores of 1, 5, 20 are given to slightly soiled, moderately soiled, and saturated pad, respectively. Score 1 is given to the small clot and 5 to the large clot. PBAC score up to 10 is considered as scanty flow, 10–100

as moderate flow, 100–300 as heavy flow, and more than 300 as very heavy flow. PBAC score more than 100 is considered as blood loss more than 80 ml diagnostic of menorrhagia [6]. Degree of anemia was also noted. Hemoglobin level of 7–9 g % was considered as moderate anemia, 9–11 g % as mild anemia, and hemoglobin [11 g % as no anemia. P values, t score of both groups, and t score of group A versus group B were calculated.

RESULTS:

There were a total of 100 patients in our study. 54 patients were in group A and 46 patients were in group B. Mean age in group A was 38.16 ± 6.8 years, while in group B, it was 35.5 ± 6.9 years. Mean parity

of group A was 3.9 ± 0.95, while that of group B was 3.4 ± 1.2. No statistical difference was found between age and parity distribution in both the groups...

Table 2 Pre- and post-treatment amount of blood loss

Menstrual pattern	Pretreatment group A *n%*	Pretreatment group B *n %*	1st follow up group A *n%*	1st follow up group B *n%*	2nd follow up group A *n %*	2nd follow up group B *n%*
Amenorrhea	0(0)	0(0)	16(30)	5(12)	8(14.1)	2 (4)
Scanty flow	0(0)	0(0)	3(6.2)	4(8)	0(0)	6(12)
Moderate flow	4(6.7)	2(4)	21(40.4)	9(20)	36(66.7)	29(63)
Heavy flow	18(33.3)	22(48)	11(20.8)	15(32)	5(9.1)	3(5)
Very Heavy flow	32(60)	22(48)	3 (6.7)	13(28)	5(10)	6(12)
total	54	46	54	46	54	46

Incidence of amenorrhea was more in group A than that in group B after treatment. The effect of the drug on group B developed gradually (less efficient): at first follow-up only 19(41.6 %) patients had blood loss <80 ml, but at the second follow-up 36 (83.3 %) had blood loss <80 ml (similar efficacious to ormeloxifene). In group A, at first follow-up, 46 (82.1 %, more efficient than MPA) patients were relieved of menorrhagia, and at the second follow-up 48 (86.6 %, similar efficacious to MPA) patients had blood loss<80 ml.

Table 3 Comparison of clinical characteristics of pre- and post-treatment between both the groups

Clinical characteristics	Group A			Group B		
	Pre t/t	Post t/t	*t* score (p value)	Pre t/t	Post t/t	*t* score (p value)
Mean duration of beeding (days)	9	4.8		8.7	5.0	
Median PBAC score (range)	365 (115-800)	75 (0-600)	9.5 (<0.001)	300 (100-650)	75 (0-480)	7.6 (<0.001)
Mean heamoglobin gm%(range)	8.6 (+/-0.86)	9.8 (+/-0.72)	10.3 (<0.001)	8.7 (+/-0.72)	9.9 (+/-1.6)	7.9 (<0.001)
Mean endometrial thickness (range)	7.71 (+/-0.93)	6.8 (+/-2.4)	2.9 (<0.05)	7.4 (+/-1.6)	6.9 (+/-1.6)	2.5(<0.05)
Numberof women with passage of clots	40 (73.3%)	7 (13.3%)		30(64%)	7 (16%)	
Number of women with lack of response	5(10%)			5(12%)		

t/t – treatment

The mean duration of bleeding was 9 and 8.7 days before treatment which was reduced to 4.8 and 5 days after 4 months of treatment in group A and group B, respectively. The reduction in median PBAC score was 79.4 % in group A and 75 % in group B after 4 months of treatment. The reduction was statistically significant in both the groups. The increment in mean hemoglobin was 1.4 g % in group A and 1.2 g % in group B after treatment, which was also statistically significant in both the groups. After treatment, a statistically significant reduction in mean endometrial thickness was seen in both the groups (0.91 mm in group A and 0.5 mm in group B).

In our study, 5 patients showed a lack of response after 4 months of treatment with ormeloxifene. The mean PBAC score of these patients was 446 before treatment which reduced to 310 (30.4 % reduction) and 460 (3.1 % increment) after 2 and 4 months of treatment, respectively. Initially, they showed good response at 2 months of treatment but they again developed increased blood loss after 4 months. Out of 5, 1 had simple endometrial hyperplasia initially and on repeat biopsy they showed complex hyperplasia without atypia. One patients underwent hysterectomy by their choice .

After treatment with medroxyprogesterone, 12 (28 %) and 5(12 %) patients showed a lack of response after 2 and 4 months of treatment. The mean PBAC score of these patients was 422 before treatment which increased to 424 (0.47 % increment) and 433.3 (2.7 % increment) after 2 and 4 months of treatment, respectively. All of them showed no response throughout the treatment period. Two patients underwent hysterectomy during treatment period in this group. Three patients were lost to follow up

Table 4 Comparison between group A and group B

Pre-treatment – post-treatment difference	Group A versus Group B *t* score
Mean PBAC score	*t* = 0.18 (not significant)
Mean hemoglobin	*t* = 0.32 (not significant)
Mean endometrial thickness	*t*=0.18(not significant)
Reduction in passage of clots	*t* = 0.16 (not significant)
Failure rate	χ^2= 0.2 (not significant)

The differences in pre-treatment and post-treatment values are statistically significant in each group, but no statistical significant difference was found between the effects of both the drugs. Effect of ormeloxifene in AUB was comparable to medroxyprogesterone in terms of reduction in passage of clots, reduction in PBAC score, improvement in hemoglobin concentration, and reduction in endometrial thickness

No major side effects were seen in our study in both the groups. In group A, 7 (13.3 %) patients developed cervical discharge, and 3 (6.7 %) patients developed vague abdominal pain. In groupB,7 (16 %) patients complained ofweight gain, 9 (20 %) patients complained of intermenstrual spotting, and 3 (8 %) patients developed dyspepsia.

DISCUSSION:

The results of this study are comparable to other studies also. Incidence of amenorrhea was reported to be 9.5 % in a study by Sharvage et al. [8], while Komaram et al. [9] found it to be 10 %. We found incidence of amenorrhea to be 14.1 % in our study. In a double-blind randomized controlled trial of ormeloxifene versus MPA in dysfunctional uterine bleeding (DUB), Shravage et al. found that the reduction in the mean PBAC score was 85.71 % with ormeloxifene and 54.76 % with MPA after 4 months of treatment [8]. The result with ormeloxifene is nearly similar to our study (79.4 %), but the result with MPA in their study was less efficacious than ormeloxifene. The reason may be the insufficient dose of MPA. They administered only 10 mg of MPA daily, while we gave 20 mg daily for 21 days. Komaram et al. [8] found that the mean endometrial thickness was reduced from 11.67 mm to 9.3 mm (20.3 % reduction) after 4 months of treatment, which is more than our study (11.6 % reduction). The reason might be that their pre-treatment endometrial thickness was also higher than our study. In a study by Kriplani et al. [5], the mean hemoglobin was increased to 11.2 g % from 10.6 g %, while Komaram et al. [9] found an increment in hemoglobin from 9.2 to 10.5 g %. These results are similar to that of our study. We concluded from this study that ormeloxifene being a non-steroidal drug should be considered the first choice in the management of AUB, especially in the perimenopausal age group where amenorrhea is acceptable. Weaknesses of this study are relatively small duration of follow-up and non-randomization, but still our results are reliable because of sufficient sample size,

excellent patient registry, and strict adherence to assessment method. A large randomized controlled trial is needed to further validate the results by comparing its efficacy and efficiency with other hormonal preparation.

CONCLUSION :

As per this study that ormeloxifene being a non-steroidal drug should be considered the first choice in the management of AUB, especially in the perimenopausal age group where amenorrhea is acceptable.

Compliance with Ethical Standards:

Conflict of interest The authors declare that they have no conflict of interest regarding this study and its publication.

Ethical approval The study was conducted in the Department of Obstetrics and Gynecology of Santhiram Medical College,Nandyal, N.T.R University of Health Sciences from Febrauary 2021 to July 2021with an informed consent and approval from the institutional ethical committee.

Informed consent Informed consent was obtained from all patients and hospital ethical board for study

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