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Role of Ormeloxifene in Abnormal Uterine Bleeding-A Prospective Study

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Abstract

Abnormal uterine bleeding (AUB) is a major gynecological problem in women of reproductive age group. This study was done to determine the efficacy and safety of ormeloxifene in AUB. Eighty women who fulfilled the inclusion and exclusion criteria were enrolled in this prospective clinical study and were given ormeloxifene 60 mg twice weekly for first three months and then once weekly for next 3 months. The outcome was studied at 0, 3 and 6 months of treatment, by assessing the mean blood loss by pictorial blood assessment chart score (PBAC score), haemoglobin and endometrial thickness. The side effects were also noted. The mean blood loss (PBAC score) at 0, 3 and 6 months was 304 ± 90.22, 108.87±73.85 and 47.55±36.78 respectively. The difference was statistically significant (p value<0.001). There were no major side effects. It is concluded that ormeloxifene is an effective and safe therapeutic option for the medical management of AUB.

Keywords: Ormeloxifene; Abnormal Uterine Bleeding

Abbreviations

AUB: Abnormal Uterine Bleeding; PBAC: Pictorial Blood Assessment Chart; SERM: Selective Estrogen Receptor Modulator; PCOD: Polycystic Ovarian Disease; IUCD: Intrauterine Contraceptive Device; Hb: Hemoglobin; ET: Endometrial Thickness.

Introduction

The prevalence of Abnormal uterine bleeding (AUB) in India is 17.9% [1]. AUB is responsible for 20-30% visits to gynaecology outpatient clinics amongst women in reproductive age group and 69 % in a peri- or postmenopausal group. There are various drugs used in the treatment of AUB such as antifibrinolytics, combined oral contraceptives, progesterones, levonorgestrel intrauterine system, danazol, gonadotropins releasing hormone, etc., but every treatment option has its own benefits and risks. Some of these are very costly and some can be used only for a limited period of time. Nonetheless worldwide, AUB is a very common indication of hysterectomy in women of perimenopausal age. Ormeloxifene is a 3rd generation Selective estrogen receptor modulator (SERM). It is a non- steroidal, non-hormonal oral contraceptive developed by the Central Drug Research Institute, Lucknow. It is available in Indian markets as 'Saheli' since 90's [2]. It is primarily a potent estrogen antagonist which normalizes the bleeding from uterine cavity by regularizing the expression of estrogen receptors on endometrium. Moreover, it has some estrogenic activity on lipid metabolism, bone mineral density and vagina [3,4]. It also has a potent antiproliferative effect on the breast tissue.

Though primary use of ormeloxifene is as a contraceptive agent (dose of 30mg twice weekly for first 3 months and then once weekly thereafter), it is increasingly being used in the management of mastalgia & even breast cancers [5]. There is no evidence of serious adverse events and no serious ovarian pathology. Additional benefits are that it also decreases total cholesterol and LDL cholesterol levels by about 20-30% [6]. While using ormeloxifene as a contraceptive, it was observed that there was decrease in menstrual bleeding in amount and duration. This side effect can be utilized as an effect to treat AUB and the weekly dosage schedule is also an advantage to women. Hence this study was planned to see the efficacy and safety of ormeloxifene in treatment of AUB.

Objectives

1. To study the efficacy of ormeloxifene in terms of decrease in menstrual blood loss as assessed by decrease in pictorial blood assessment chart score (PBAC score), hemoglobin improvement, and decrease in endometrial thickness.
2. To study any major or minor side effects.

Methodology

This was a prospective interventional study done for 18 months (2019 to 2020) in the outpatient department of Obstetrics and Gynaecology, Bhagat Phool Singh Government Medical College, Khanpur Kalan, Sonepat, Haryana. The inclusion criteria were women of age 21-50 years with heavy menstrual bleeding, intermenstrual bleeding or frequent cycles/ short cycles with PBAC score >100, uterine size ≤ 8 week and intramural fibroid if any ≤ 2.5 cm size. The women excluded from study were those with postmenopausal bleeding, genital malignancy, acute heavy bleeding, history or clinical evidence of hepatic/ renal disease, PCOD, any organic pathology e.g. intramural fibroid > 2.5 cm, uterine size > 8-week size, endometriosis, polyp, adenomyosis, IUCD, oral contraceptive pill and other hormonal contraceptives users, thyroid disorder, abortions within 3 months and lactating women in 1st 6 months of post-natal period. The sample size was calculated using following formula: N = (Zα/2 + Zβ) 2 * (SD * 2) / d2. After adjusting for loss to follow up, we enrolled 80 eligible consecutive patients fulfilling the inclusion and exclusion criteria from the Obst and Gynae OPD. The study was approved by institutional ethical committee (Registration number-BPSGMCW/ RC 419/ IEC /19). Women were treated with ormeloxifene 60 mg twice weekly for first 3 months and then once weekly for next 3 months and results were evaluated on follow up.

The following outcome variables were studied:

1. Menstrual flow in days and menstrual cycle length.
2. Pictorial blood loss assessment chart score (PBAC score): It is used for objective assessment of menstrual blood loss. Number of sanitary pads used each day of menses were counted. For sanitary napkin; a score of 1 for lightly stained, 5 for moderately soiled and 20 for completely soiled pad was used. A score of 1 was given for small Clots, 5 for large clots and 5 for each episode of flooding. Total score was calculated by adding all the scores used in a menstrual cycle. Heavy menstrual bleeding is equal to >80 ml of menstrual blood loss which correlates with PBAC score >100 [7].
3. Hemoglobin (Hb): It was done in the Central Laboratory, Pathology department using the automated analyzer.
4. Endometrial thickness (ET) (premenstrual): A transvaginal sonography was done for endometrial thickness and any other pathology.
5. Side effects of ormeloxifene: These were assessed on each follow-up.

Data were collected using a pre-designed semi-structured study proforma. Consecutive 80 women in reproductive age who presented to outpatient department with complaints of frequent heavy cycles and who fulfilled inclusion and exclusion criteria were enrolled for study after written informed consent and detailed history, gynecological examination and investigations were done. The haemoglobin, PBAC score and endometrial thickness were assessed at 0, 3 and 6 months:

The analysis included profiling of patients on different demographic, laboratory and clinical parameters. Descriptive analysis of quantitative parameters was expressed as means and standard deviation. Ordinal data were expressed as absolute number and percentage. Repeated measure ANOVA test was used to analyze the difference in hemoglobin, PBAC score and endometrial thickness at each follow up. P-value < 0.05 was considered statistically significant. All analyses were done using SPSS software, version 30. It is declared that all the research conducted in the present study is in accordance with the principles set forth in the Helsinki Declaration 2008.

Results

Table 1 depicts the demographic profile of the patients and most of the patients i.e., 93.75 % were more than 30 years of age. The mean age was 38.93 ± 5.90 years (range 26 to 49) and the mean parity was 2.65±0.75 (range 2 to 4). The mean BMI was 27.40±3.382 kg/m2 (range 19.4 to 37.7) and majority i.e., 67.5% patients belonged to rural area. Moreover, most of the patients (52.5%) belonged to upper middle class. Figure 1 shows the PBAC chart and Figure 2 depicts how the patients were recruited and followed in the study. 80 patients were recruited in the study. There were 11 patients who stopped treatment after 3 months, of which only 3 patients had responded to treatment. Of the 8

non-responders, 6 underwent hysterectomy, one changed to other medical treatment and one was lost to follow-up. Total 69 patients were followed up for 6 months, of which 66 responded to treatment.

PBAC SCORING

Name of patient	Days							Score
Sanitary Pads	1	2	3	4	5	6	7	
								
								
								
Tampons								
								
								
								
Clots/Flooding								
1 Point	For each small clot (Australian 5 cent coin)							
5 Points	For each largel clot (Australian 50 cent coin)							
5 Points	For each episode of flooding							

1= Lightly stained

5=Moderately stained

20= Completely stained

1= Lightly stained

5=Moderately stained

10= Completely stained

Figure 1: Pictorial Blood Assessment Chart (PBAC) scoring for uterine bleeding [8].

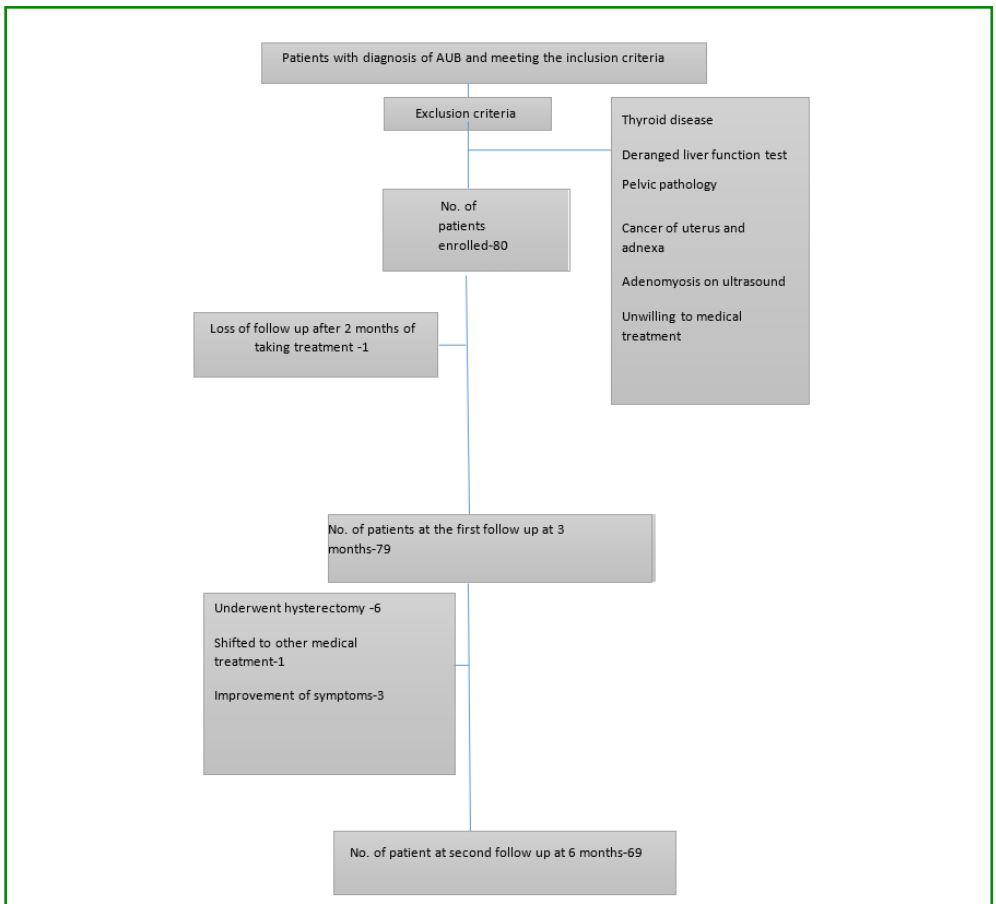

Figure 2: Disposition tree showing details of patients recruited and loss to followup.

S.No.	Demographic characteristics	Groups	N=80 (%)
1	Age (years)	21-30	5 (6.25)
		31-40	42 (52.5)
		41-50	33 (41.25)
2	Parity	2	39 (48.75)
		3	30 (37.5)
		4	11 (13.75)
3	BMI (Kg/m^2)	18.5-24.9	15 (18.75)
		25-29.9	48 (60)
		≥30	17 (21.25)
4	Residential status	Rural	54 (67.5)
		Urban	26 (32.5)
5	Socioeconomic status	Upper	0 (0)
		Upper middle	42 (52.5)
		Lower middle	26 (32.5)
		Upper lower	12 (15)
		Lower	0 (0)

Table 1: Distribution of patients according to demographic profile.

Table 2 shows the pattern of AUB among the patients at the time of enrollment in the study and then at 3 and 6 months after treatment. In 85% patients the pretreatment menstrual days were 4- 9 days and at 3 months and 6 months post treatment only 55.7% patients and 15.9% patients respectively had 4-9 days of menstrual days. More over menstrual days reduced to 1-3 days at 3 months and 6 months post treatment in 36.7% patients and in 56.52% patients respectively. The reduction in number of menstrual days was statistically significant at 3 months and 6 months (p value-0.000). The pretreatment menstrual cycle length of 21- 30 days was present in 55% patients. At 3 months post treatment the menstrual cycle length of 21- 30 days was seen in 26.6 % patients and at 6 months 5.8% patients only. Pretreatment menstrual cycle length of 31-40 days was present in 2.5% patients. Post treatment patients in menstrual cycle length of 31- 40 days group increased to 65.8% at 3months and 65.2% at 6 months. Thus, the increase in length of menstrual cycle was statistically significant at 3 months and 6 months (p value-0.000).

S.No.	Variable	Groups	Pre-treatment N=80(%)	At 3 month s N=79(%)	At 6 months N=69(%)	P value [a]
1	Menstrual days	Amenorrhea	0(0)	6(7.6)	19(27.54)	0.000-0.001
		3-Jan	0(0)	29(36.4)	39(56.52)	
		9-Apr	68(85)	44(55.7)	11(15.94)	
		≥10	12(15)	0(0)	0(0)	
2	Menstrual cycle length in days (%)	Amenorrhea	0(0)	6(7.6)	19(27.5)	
		20-Jan	34(42.5)	0(0)	0(0)	
		21-30	44(55)	21(26.6))	4(5.8)	
		31-40	2(2.5)	52(65.8)	45(65.2)	
		40-50	0(0)	0(0)	1(1.5)	

3	PBAC score (%)	<50	0(0)	7(8.9)	26(37.68)	
		51-100	0(0)	45(56.9)	40(57.97)	
		101-200	10(12.5)	18(22.8)	2(2.9)	
		>200	70(87.5)	9(11.4)	1(1.45)	
4	Hb in gm/dl (%)	<7	2(2.5)	0(0)	0(0)	
		7-8.9	45(56.25)	11(13.9)	7(10.14)	
		9-10.9	32(40)	59(74.7)	51(73.92)	
		≥11	1(1.25)	9(11.4)	11(15.94)	
5	ET in mm (%)	<5	1(1.25)	14(17.7)	26(37.68)	
		10-May	70(87.5)	64(81)	42(60.87)	
		≥11	9(11.25)	1(1.3)	1(1.45)	

A Pairwise comparisons were done by repeated measure ANOVA for menstrual flow days in a month, menstrual cycle length, PBAC score, haemoglobin and endometrial thickness. Comparisons of above said parameters were made between pretreatment and 3 months pair, 3 months and 6 months pair and pretreatment and 6 months pair. The p value of all comparisons was highly significant i.e., 0.000-0.001.

Table 2: Distribution of patients according to various parameters before and after treatment.

The mean PBAC score pre-treatment, 3 months and 6 months was 304 ± 90.22, 108.87±73.85 and 47.55±36.78 respectively. Pretreatment PBAC score of > 200 was present in 87.5% patients. Post treatment PBAC score of >200 was present in 11.4% patients at 3 months and in only 1.45% at 6 months. The reduction in PBAC score was statistically significant at 3 months and 6 months (p value<0.000). The pre-treatment, 3months and 6 months mean Hb was 8.78±0.95 gm%, 9.77±0.92 gm% and 10.07±0.94 gm% respectively. It was also observed that ≥ 11 gm% Hb was present only in 1.25% patients before treatment. At 3 months 11.4% patients and at 6 months 15.94% patients had Hb level ≥11gm%. The increase in Hb level was also statistically significant at 3 months and 6 months (p value-0.000). The pre-treatment, 3 months and 6 months mean endometrial thickness was 8.39±1.74 mm, 5.94±1.48 mm and 5.44±1.99 mm respectively. Endometrial thickness was < 5 mm in 1.25% before treatment, at 3 months 17.7% patients and at 6 months 37.68% patients had endometrial thickness < 5 mm. And the decrease in endometrial thickness was also statistically significant at 3 months and 6 months (p value-0.001).

It was observed that nineteen (23.75%) patients developed amenorrhea (6 after 3 months of treatment and 13 after 6 months of treatment). Five (6.25%) patients had occasional nausea, 4 (6.25) patients had ovarian cysts, 2 patients had headache, 1 patient had cervical erosion and 1 patient had vague abdominal pain. But none of these led to stoppage of treatment.

Discussion

AUB is a major gynecological problem of perimenopausal age and is a common cause of hysterectomy. Ormeloxifene is a very popular contraceptive in India and is being used since 1992. The side effect of this drug is oligomenorrhoea and hypomenorrhoea which may be utilized to treat AUB. Ormeloxifene reduces up to 70 % blood loss and has a faster response which makes it a good option in medical management of AUB [8].

Like the present study Gaur and Chawla et al have also reported reduction in the menstrual flow in days in a cycle as well as increase in cycle length at 3 and 6 months after treatment [9,10]. The incidence of amenorrhoea was 23.75% (19/80) in the present study and it was 9.5 % in a study by Sharvage et al. while Komaram et al. found it to be 10 % [11,12].

In the current study the mean PBAC score reduced significantly at 3 months and 6 months from 304 ± 90.22 to 108.87±73.85 and 47.55±36.78 respectively (p value-0.000). Similarly in the study by Mani et al, it was reduced significantly from 175.3 to 51.2 & to 20.9 (p value < 0.0001) after 3 and 6 months in proliferative endometrium and from 179.2 to 48.4 and 14.8 (p value < 0.0001) after 3 & 6 months respectively in secretory endometrium [13]. In another study by Kaur et al, PBAC score decreased from the basal value (pretreatment) of 244.16± 37.71 to 143.09 ± 36.40 at 3 months and 96.33 ± 25.67 at 6 months (p<0.001) [14]. Similar other studies by Kriplani et al, Chawla et al and Kumari et al also reported a significant reduction in Mean blood loss and PBAC score [9,11,16].

In the present study the pre-treatment mean hemoglobin level was 8.78±0.95 gm%. Post treatment Hb at 3 months

was 9.77±0.92 gm% and 10.07±0.94 gm% at 6 month. The increase in Hb level was statistically significant at 3 months and 6 months (p value-0.000). In a study by Kaur et al, mean hemoglobin levels increased to 8.90 ± 0.83 gm/dl at 3 months and 9.69 ± 0.90 gm/dl at 6 months from the pretreatment value of 8.11±0.74 gm/dl [14]. The increase in mean hemoglobin levels was highly significant statistically, on post treatment at three months and six months, (p<0.001, significant). Other authors Mani et al, Kumari et al and Gandotra et al have reported similar findings [13,15,16]. Author Mani et al have categorized that effect of ormeloxifene on proliferative, secretory and atrophic endometrium according to the histopathology of endometrium and found that in atrophic endometrium cases Hb level increased slightly from 7.8gm/dl to 8.3gm/dl (p value < 0.5) after 3 months of treatment but again decreased to 6.8gm/dl (p value 0.6) after 6 months of treatment with ormeloxifene. They suggested that probably ormeloxifene doesn't work well in patients with atrophic endometrium [13]. But no such effect of first increase and then decrease in Hb was found in the present study.

In the present study the pre-treatment mean endometrial thickness was 8.39±1.74 mm (range 4 to 14). At 3 months and 6 months mean ET was 5.94±1.48 mm and 5.44±1.99 mm. Thus, the decrease in endometrial thickness was statistically significant at 3 months and 6 months (p value-0.001). Kumari et al reported that the mean endometrial thickness at the beginning of treatment was 11.81 mm, which was reduced to 7.63 mm at 6 months showing a marked reduction of 4.18 mm (35.39%) from its pre-treatment level.15 Gandotra et al also reported that pre and post treatment mean endometrial thickness was 10.8mm and 8.1mm respectively with a significant decrease of 2.7mm (p value<0.05) [16,17].

The eight patients who did not have improvement in their symptoms of heavy menstrual bleeding and who later shifted to either OCP's or hysterectomy, it was observed that their BMI was between 25-32 kg/m2 (p value -0.016). A high BMI may be the reason for having no response to treatment as a higher dose would have been required. Moreover, their pretreatment PBAC score was between 217-412 (p value-0.746) and their pretreatment endometrial thickness was 6.8 - 9 (p value- 0.556).

Similar to the present study most studies reported minor side effects like small ovarian cysts, vague abdominal pain, headache, weight gain and spotting but none lead to stoppage of treatment [9,10,14,15].

Conclusion

It is to conclude from this study that ormeloxifene is a non-hormonal drug with fewer and non-significant side effects and it should be considered as the drug of choice in AUB. In developing nations like India cost of treatment is an important factor since LNG IUS and oral progesterones are not afforded by most. Additionally the twice a week schedule is a significant advantage over the daily schedule of progesterones. There are few Indian studies and almost no foreign studies of use of ormeloxifene in AUB. Further larger and randomized studies may be planned for its comparison with LNG IUS and progesterones to validate its efficacy and safety so that the women of entire world can take advantage of ormeloxifene.

Strengths and limitations of the study- Strength of this the study is that a very common gynecological problem of abnormal uterine bleeding is taken up in this article. Development of newer drugs or exploring the scope of existing drugs is imperative to save the women from unnecessary hysterectomies which lead to early menopause and its related complications. However, the results would have been more emphatic had it been a comparative study.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Ethical Approval

From institutional ethical committee approval was taken. Approval number-BPSGMCW/ RC 419/ IEC /19.
Patient consent: informed and written consent was taken from each participant who agreed to participate in the study.

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