Research Article

Role of ormeloxifene, a selective estrogen receptor modulator in heavy menstrual bleeding (abnormal uterine bleeding)

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Received: June 21, 2018; **Accepted:** July 11, 2018

ABSTRACT

Background: During women's reproductive years, heavy menstrual bleeding (HMB) (abnormal uterine bleeding; AUB) is the most common reason for abnormal vaginal bleeding. Evidence is lacking for medical management of HMB (AUB). Ormeloxifene a selective estrogen receptor modulator (SERM) has emerged as one of the safe and effective candidates for the management of HMB (AUB). **Objectives:** The objectives of this study were to study the efficacy and safety of SERM, ormeloxifene in the treatment of HMB (AUB). **Material and Methods:** A total of 65 patients of HMB (AUB) were studied in the Department of Obstetrics and Gynecology, GR Medical College, Gwalior, from September 2011 to December 2013. Detailed history, clinical examination, and laboratory investigations including hemoglobin percentage, blood sugar, pap's smear, transvaginal ultrasonography, and dilatation and curettage were recorded for each patient. Tablet containing 60 mg of ormeloxifene was given for twice a week for first 12 weeks then 60 mg once a week for next 12 weeks. All the patients were followed up for 6 months till the 6 months. **Results:** Maximum patients had age between 31 and 40 years (46.5%). The most common parity was one to three (53.4%). Most of the cases complained of menorrhagia (41.8%). Majority of the cases showed proliferative endometrium (49.18%). Of 65, 5 could not be followed up due to various reasons. At 12 weeks of treatment, most of the cycles exceeded their pretreatment cycle length; improvement in duration of blood flow and dysmenorrhea (from 76.7% case to 19%) was observed; spotting and passage of clots were not observed in 58% by 12 weeks and 96% patients by 24 weeks. Most frequent side effects complained by patients were prolonged cycle beyond 35 days (50%). **Conclusion:** Ormeloxifene is a good choice for the treatment of HMB (AUB) due to its excellent efficacy and safety profile.

KEY WORDS: Dysmenorrhea; Endometrium; Ormeloxifene; Selective Estrogen Receptor Modulator

INTRODUCTION

Heavy menstrual bleeding (HMB) (abnormal uterine bleeding; AUB) can be defined as abnormal, irregular, and genital tract bleeding in the uterus and can be detected in the absence of demonstrable structural or organic pathology.[1] HMB (AUB) is one of the common reasons for the abnormal vaginal bleeding during a woman's reproductive years.[2]

Access this article online	
Website: http://www.ijmsph.com	**Quick** Response code
DOI: 10.5455/ijmsph.2018.0720111072018	

Pathophysiology of HMB (AUB) is not known, but it takes place in both ovulatory and anovulatory menstrual cycles. Several local factors are reported to be involved in the control of menstrual blood loss and any abnormality in these factors can lead to menorrhagia. HMB (AUB) most of the time is the result of endocrinological dysfunction which usually responds well to the conservative treatment.[3]

Numbers of option are available for the treatment of HMB (AUB), but a reliable drug modality in the management has to be effective, low cost and has minimal side effects. Selective estrogen receptor modulator drugs (SERM) are well known as designer estrogens as it has high affinity toward the receptor and is selective in nature.[4]

Ormeloxifene is the example of such SERM available for the treatment of HMB (AUB).[5] It arbitrates its action due to high-affinity interaction with estrogen receptor.[6] Ormeloxifene is the only preferred oral contraceptive which can effectively treat the HMB (AUB). Standard dose of ormeloxifene is 60 mg orally twice weekly for a period of 12 weeks followed by weekly once in the next 12 weeks. Nevertheless, ormeloxifene antagonize estrogen in uterus (endometrium), breast tissues which result in endometrial atrophy to decreases menstrual blood loss.[4-6]

Data on the safety and efficacy parameters of ormeloxifene are limited; hence, the present study was designed to evaluate its safety and efficacy for the treatment of HMB (AUB).

MATERIALS AND METHODS

A prospective study was done on 65 cases of HMB (AUB) attending the outpatient clinic and those admitted in Kamala Raja Hospital in Department of Obstetrics and Gynecology, GR Medical College, Gwalior, from September 2011 to December 2013.

Institutional Ethics Committee approval and written informed consent from each patient was obtained before commencing study.

Patients in all age group with abnormal menstrual bleeding without any detectable pathology or any organic lesions were included in the study. Women with pregnancy, bleeding due to pregnancy complications such as vesicular mole, or abortions, lactating mother, acute heavy bleeding necessitating emergency treatment, adenomyosis, endometriosis, fibroid, uterine size more than 8 weeks, adnexal mass, malignancy of breast or genital tract, diabetes, chronic hypertension, blood dyscrasias, thyroid dysfunction, psychological disorders, and liver, renal, and heart disease were excluded from the study.

After taking thorough history including presenting complaint, menstrual history, obstetric history, and past medical and surgical history, patients were subjected to routine clinical examination (general, systemic, breast, and gynecological examination) followed by laboratory investigations (hemoglobin percentage, blood sugar, pap's smear, transvaginal ultrasonography, and dilatation and curettage) and follow up for 6 months (duration of bleeding, amount of bleeding, cycle length, passage of clots, dysmenorrhoea, spotting, appearance of any side effect, general and systemic examination, breast examination, and gynecological examination). The cases were subjected to dilatation and curettage at the initiation of the study, material sent for histopathological examination of the endometrium.

Doses and schedules: Tablet containing 60 mg of ormeloxifene was given for twice a week for first 12 weeks then 60mg once a week for next 12 weeks.

RESULTS

Of 65 cases, maximum patients belong to 31–40 years (46.5%), followed by 21–30 years (27.9%) and overall age range was between 18 and 53 years. Only 2 (2.3%) patients were of age of >50 years. Majority of the cases were parous women, whereas 6 (9.3%) women were nulliparous. Among parous women, 35 (53.4%) cases belong to para 1–3 and 24 (37.2%) cases were of parity more than 4. Majority of the cases complained of menorrhagia 28 (41.8%), and 18 (27.9%) had menometrorrhagia. Five cases were unmarried and were not subjected to dilatation and curettage. Of 61 cases, 30 (50%) showed proliferative endometrium (30 [49.18%]), 23 (37.5%) had secretary endometrium and 6 (10%) showed mixed pattern. Of 65 cases, five cases were excluded from analysis (two found hypothyroid after 1 month, two patients had prolonged cycles of more than 40 days after 3 months of treatment, and one patient underwent hysterectomy after 4 months). Hence, 60 (92.3%) patients were followed up for 6 months. There was the reduction by 17.6% in the mean bleeding with 12 weeks of treatment and 33.8% reduction in the mean bleeding days by 24 weeks. Only 16 patients reported minor side effects, most frequent being prolonged cycle beyond 35 days (8 [50%]), 3 (18.75%) had prolonged of cycle by 3rd month and lost in the follow-up. Six (37.550) had mild abdominal pain throughout the cycle, 1 (6.25%) had significant weight gain above the pre-treatment weight [Table 1].

DISCUSSION

HMB (AUB) usually occurs in the first 5 years after menstruation is started and as women approach menopause, but it can occur at any age.[2] Women with HMB (AUB) who wish to retain fertility; pharmacological treatment is the only available option.[8,9] In the present study, we have analyzed the efficacy and safety of ormeloxifene in patients with HMB (AUB) and our findings showed a significant reduction in menstrual blood loss with minimal side effects.

Results are similar to recent study from Srinagar by Khan *et al*. including 50 patients with HMB (AUB) which also showed significant reduction in menstrual blood loss with the ormeloxifene treatment with 99.7% reduction in blood loss.[2] Study from Allahabad, Uttar Pradesh by Singh *et al*. on 172 patients reported improvement in patients in term of

Table 1: Different parameters among the study cohort before and after treatment

Parameters	Pre-treatment	After 1 month (*n*=65)	After 2 months (*n*=63)	After 3 months (*n*=63)	After 6 months (*n*=60)
Cycle length (days)					
<10	1 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)
10–15	11 (16.2)	13 (18.6)	1 (2.2)	0 (0)	0 (0)
16–20	22 (34.8)	21 (32.5)	20 (30.9)	3 (4.7)	0 (0)
21–25	5 (6.9)	4 (4.06)	10 (16.6)	10 (16.6)	0 (0)
26–30	21 (32.5)	22 (34.8)	22 (34.8)	36 (57.3)	42 (72.5)
31–35	3 (4.6)	4 (4.6)	5 (7.1)	8 (11.9)	10 (15)
>35	1 (2.3)	1 (2.3)	5 (7.1)	6 (9.5)	8 (12.5)
Duration of flow (days)					
2–4	21 (32.5)	19 (30.2)	20 (30.9)	23 (38)	35 (57.5)
5–8	19 (30.2)	21 (32.5)	25 (40.4)	30 (47.6)	25 (42.5)
9–10	14 (20.9)	14 (20.9)	11 (16.6)	9 (14.2)	0 (0)
>10	11 (16.2)	11 (16.2)	7 (11.9)	0 (0)	0 (0)
Bleeding (days)					
Total	440	411	396	354	270
Mean	6.8	6.5	6.2	5.6	4.5
Amount of blood flow					
Heavy	47 (72)	47 (72)	39 (61.9)	15 (23.8)	2 (2.5)
Normal	18 (28)	18 (28)	24 (38.1)	48 (76.1)	58 (97.5)
Dysmenorrhea incidence					
Present	50 (76.7)	50 (76.7)	27 (42.8)	12 (19.04)	6 (10)
Absent	15 (23.2)	15 (23.2)	36 (57.1)	51 (80.9)	54 (90)
Presence of clots*					
Present	50 (76.7)	50 (76.7)	38 (59.5)	21 (33.4)	2 (3.3)
Absent	15 (23.2)	15 (23.2)	25 940.4)	42 (66.6)	58 (96.6)
Spotting#					
Present	24 937.2)	24 937.2)	6 (9.5)	3 (4.7)	2 (2.5)
Absent	41 (62.7)	41 (62.7)	57 (90.4)	60 (95.2)	58 (97.50
Bleeding control					
Excellent	0 (0)	0 (0)	0 (0)	16 (23.8)	42 (70)
Good	0 (0)	15 (23.2)	17 (26.2)	22 (35.7)	15 (25)
Poor	60 (100)	50 (76.4)	46 (73.8)	25 (40.4)	3 (5)

*Presence of clots in menstrual blood during treatment cycle, #presence of spotting (pre-menstrual and post- menstrual) during treatment cycle. Data are expressed as number of patients (percentage) until and unless specifically specified

absence of dysmenorrhea after treatment using ormeloxifene which blocks the action of progesterone.[10,11] Prostaglandins, especially prostaglandin F2-alfa and vasopressin and endothelins, stimulate myometrial contraction which is released by endometrium during menstruation.[12] Optimal level of estrogen is necessary or action of progesterone. Hence, higher level of progesterone increases prostaglandins which cause pain during menstruation; known as dysmenorrhea.[13] Komaram *et al*. studied 50 women with HMB (AUB) at Visakhapatnam, Andhra Pradesh, reported significant improvement, 84% had a relief from dysmenorrhea which again confirms the efficacy of the drug for the treatment of HMB (AUB). Komaram *et al* did not find any major adverse event which is in accordance to the present study data.[4] Srilakshmi *et al*. concluded that oral administration of ormeloxifene alleviates patient's compliance and acceptability. They also reported a marked increase in the relief of symptoms resulting in higher satisfaction.[7]

The small sample size was the main limitation of the present study; a large clinical trial is needed to strengthen the present study results.

CONCLUSION

It is concluded from the results that ormeloxifene is helpful in the management of HMB (AUB) with an excellent safety profile, good acceptability, and minimal side effects. There

was marked improvement in duration of flow, dysmenorrhea, spotting, and passage of clots with regularization of the cycles. However, the long-term effects are still to be observed.

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How to cite this article: Gaur Y, Parashar H, Jain S. Role of ormeloxifene, a selective estrogen receptor modulator in heavy menstrual bleeding (abnormal uterine bleeding). Int J Med Sci Public Health 2018;7(10):834-837.

Source of Support: Nil, **Conflict of Interest:** None declared.