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Original Research Article

Study of efficacy of selective estrogen receptor modulator: Ormeloxifene in the management of heavy menstrual bleeding in perimenopausal patients: A prospective interventional study

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Abstract

Background: Menorrhagia is a common complaint of about 10-33% of women in perimenopausal period. Ormeloxifene is a third – generation selective estrogen receptor modulator (SERM) highly efficacious in the management of Heavy Menstrual Bleeding, but not commonly used at present.
Aim & Objective: To determine the therapeutic efficacy of SERM in management of HMB.
Materials and Methods: An institution based prospective study was conducted on 150 patients in the age group of 35-45 years who were treated with 60mg ormeloxifene twice a week for the first 3 months and once weekly for the next 3 months. The outcome was assessed based on menstrual blood loss in terms of PABC score, endometrial thickness and hemoglobin concentration.
Results: The treatment effects of ormeloxifene, in patients of Heavy Menstrual bleeding was found * PBAC score has decreased to 95 ± 28.35 in 6 months from the basal value of 244.15 ± 35.04. *endometrial thickness (in mm) has decreased to 6.70 ± 1.22 at 6 months, from the basal value of 9.57± 1.15 (mm). Haemoglobin levels have increased to 9.57 ± 0.84 at 6 months from the basal value of 7.52 ± 0.75(gm/dl).
Conclusion: Ormeloxifene is very safe, cost-effective and with manageable side effects and hence, can be used as the drug of choice in patients with HMB.

Keywords: Ormeloxifene, Heavy Menstrual Bleeding, SERM, PBAC.

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1. Introduction

Menorrhagia is one of the commonest menstrual dysfunction, affecting 10-33% of women at some stage of their lives; besides being major cause of iron deficiency anemia in females after nutritional anaemia.[1] Menorrhagia is described as heavy bleeding that occurs in cycles at regular intervals and lasts more than seven days, or more than 80 milliliters of blood loss.[2]

A variation in regularity, frequency, duration and amount of blood loss from the normal menstrual cycle without any clinically detectable organic, systemic and iatrogenic cause, is defined as Heavy Menstrual Bleeding and is a diagnosis of exclusion.[3]

To reduce symptoms and improve quality of life, treatment options for HMB vary from medical to surgical treatments, however the RCOG advice starts with medical care.[4]

Oral or intramuscular progesterone, levonorgestrel intrauterine system (LNG-IUS), anti-fibrinolytic agents like tranexamic acid, gonadotropins releasing hormone, and combined oral contraceptives pills are some available medical options.[5]

Ormeloxifene, a third-generation selective estrogen receptor modulator (SERM), is a non-steroidal, non-hormonal oral contraceptive known as SAHELI since the 1990s. It functions by exerting anti-estrogenic effects on

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uterine and breast tissue, reducing the risk of endometrial and uterine cancer. Conversely, it exhibits estrogenic effects on the vagina, bones, cardiovascular system, and central nervous system, thereby addressing issues like vaginal dryness, bone loss, and high cholesterol levels, making it particularly advantageous for perimenopausal women.

The chemical name of ormeloxifene is trans-7-methoxy-2, 2-dimethyl-3-phenyl-4 (4-(2-pyrrolidinoethoxy) phenyl (-chromanhydrochloride))[6] ormeloxifene competitively binds with cytosolic receptors and not only blocks them but also cause prolonged depletion, so that its action lasts longer even after withdrawal of drug. 60 mg of ormeloxifene is administered twice a week for the first three months and then once a week for the following three. The medication has a half-life of 170 hours and is metabolized in the liver. The uterus has the highest drug concentration, second only to the liver. Hepatic dysfunction, pregnancy, lactation, chronic disease, and PCOS are common contraindications. Weight gain, vomiting, and nausea are typical adverse effects.[7]

The aim and objective of the present study was to determine the therapeutic efficacy and efficiency of SERMS in management of HMB in perimenopausal women.

2. Materials and Methods

This is Institutional based Prospective Interventional study carried out on 35-45year old women who have H/o Heavy Menstrual Bleeding at Department of Obstetrics and Gynaecology, ACPM Medical College and Hospital, Dhule. The study duration was set for 18 months, with a 6-month recruitment period for subjects and a 12-month follow-up period.

2.1. Inclusion criteria

1. Aged 35-45 years
2. Women with H/O heavy menstrual bleeding
3. Patients who have done premenstrual D&C to rule out organic causes of bleeding.

2.2. Exclusion criteria

1. Women with % postmenopausal bleeding
2. Endometrial polyp
3. Adenomyosis
4. Cervical dysplasia
5. Uterine fibroids
6. Endometrial biopsy suggestive of atypical hyperplasia or malignancy
7. Bleeding dyscrasias
8. Clinical evidence of jaundice or hepatic dysfunction
9. Hypersensitivity to the drug.

2.3. Procedure

HMB is an exclusionary diagnosis. To exclude any other potential reason for irregular uterine bleeding, investigations were conducted. These included endometrial sampling (D and C) to rule out any pelvic disease, Pap smear, thyroid stimulating hormone, coagulation profile, total blood cell count, and pelvic ultrasound to evaluate endometrial thickness. A sample of the endometrium was sent to the pathology lab for histological diagnosis.

PBAC (Pictorial blood assessment score) Score is useful in evaluating the response of menorrhagia to different forms of treatment in a clinical setting. Using the scales mentioned below, the total score was computed by summing the scores for all sanitary napkins used during the menstrual cycle.

Ormiloxifene was prescribed using the following regimen - twice weekly for 3 months followed by once weekly for next 3 months. Follow up visits were scheduled after 3 and 6 months. During each visit a detailed menstrual history was taken, PBAC score was calculated. Haemoglobin concentration, endometrial thickness & PBAC Score were measured after 3 and 6 months of the treatment.

3. Results

Of the 150 study participants, the average age was 40.91 ± 2.82 years, with the majority of the patients (71.11%) coming from rural areas. The majority of patients in our study were literate (73.33%). Most patients have lower socioeconomic levels. The majority of the cases in the research were housewives.

Table 1: Menstrual flow (PBAC score)

Scoring	PADS
1	Lightly soiled pads
5	Moderately soiled pads
20	Severely soiled pads
	CLOTS
1	Small clots
5	Large clots
20	Flooding

Table 2: Effect of Ormeloxifene on endometrial thickness

Endometrial Thickness (mm)	Ormeloxifene Effect
Pre-treatment (Basal) (Mean ± SD)	9.57 ± 1.15
Post treatment at 3 months (Mean ± SD)	7.55 ± 1.30
Post treatment at 6 months (Mean ± SD)	6.70 ± 1.22
P value < 0.001	

The treatment effects of ormeloxifene in patients of Heavy Menstrual Bleeding - The endometrial thickness (in mm) was observed to have dropped from the basal value (pretreatment) of 9.57 ± 1.15 (mm) to 7.55 ± 1.30 at 3 months and 6.70 ± 1.22 at 6 months (post-treatment). On follow-up (post-treatment) at three and six months, the decrease in endometrial thickness was statistically very significant ($p<0.001$, significant) as shown in **Table 2**.

Table 3: Effect of ormeloxifene on haemoglobin

Haemoglobin (gm/dl)	Ormeloxifene Effect
Pre-treatment (Basal) (Mean ± SD)	7.52 ± 0.75
Post treatment at 3 months (Mean ± SD)	8.90 ± 0.79
Post treatment at 6 months (Mean ± SD)	9.57 ± 0.84
P value < 0.001	

As per **Table 3**, in individuals with heavy menstrual bleeding, the treatment impact of ormeloxifene improved hemoglobin levels from the pretreatment (base value) of 7.52 ± 0.75 (gm/dl) to 8.90 ± 0.79 at 3 months and 9.57 ± 0.84 at 6 months (post-treatment). After treatment, after three and six months, the mean hemoglobin levels increased statistically significantly ($p<0.001$, significant).

Table 4: Effect of Ormeloxifene on PBAC score

PBAC Score	Ormeloxifene Effect
Pre-treatment (Basal) (Mean ± SD)	244.15 ± 35.04
Post treatment at 3 months (Mean ± SD)	143 ± 32.17
Post treatment at 6 months (Mean ± SD)	95 ± 28.35
P value < 0.001	

Table 4 shows that ormeloxifene reduced PBAC in HMB patients from the basal value (pretreatment) of 244.15 ± 35.04 to 143 ± 32.17 at 3 months and 95 ± 28.35 at 6 months (post-treatment). At three and six months (post-treatment), the statistical significance of the PBAC score (**Table 1**) decline was $p<0.001$.

Ormeloxifene did not cause any serious side effects that would require stopping the medication, although a few patients did experience minor side effects, such as headaches in two cases, weight gain in one, spotting in three cases, and amenorrhea in seven cases. Additionally, none of the study group's patients experienced any appreciable changes in their liver or kidney functions.

4. Discussion

On average, the length of the menstrual cycle varies from 21–35 days, blood flow occurs for 2–7 days, and blood loss occurs for 20–80 milliliters per cycle. Uterine bleeding that deviates from this typical in both quantity and duration is known as dysfunctional uterine hemorrhage. We observed in our study how ormeloxifene medication affected endometrial thickness, hemoglobin, and PBAC score in individuals with dysfunctional uterine hemorrhage.

Cameron et al. showed that short-term progestogen therapy caused a non-significant reduction in MBL from 131 to 110 ml in 6 women with ovulatory menorrhagia after the treatment with norethisterone 5 mg bd from day 16 to 26 of the cycle.[8] Further work on a regimen using the same dosage from day 19 to 26 of the cycle in 15 women with ovulatory menorrhagia showed a 20% reduction in MBL from 109 to 92 ml, but two thirds of patients thus treated had post-treatment MBL >80 ml. Preston et al using norethisterone 5 mg bd from day 19 to 26 of the cycle in 21 women with confirmed ovulatory menorrhagia demonstrated a 20% increase in MBL.[9] Increasing the length of treatment to 21 days, each cycle showed improved results in one small study involving 10 patients with proven ovulatory menorrhagia.[4] In our study, ormiloxifene was prescribed using the following regimen - twice weekly for 3 months followed by once weekly for next 3 months. Follow up visits were scheduled after 3 and 6 months.

All the criteria of blood loss in HMB, such as the number of days of bleeding, the number of soiled pads, and the transit of clots, are greatly improved by ormeloxifene. Because of its few adverse effects, inexpensive cost (in comparison to all other medical and surgical therapies), and straightforward dosing schedule, the medication is not only effective but also has good patient acceptability and compliance.

In our study, the impact on the endometrial thickness of 150 patients was noted. There was a significant decrease in endometrial thickness in three months, measuring 21.10%, and in six months, it decreased by 29.98%. These results were comparable to those of a study by Khan et al., which found that endometrial thickness decreased by 23.64% in six months, and a study by Ravibabu et al., which found a reduction of 20.3%.[10,11] A study in Guwahati found that ormeloxifene is effective in reducing endometrial thickness in both proliferative endometrium from 9.6 to 4.2mm (p value 0.0001) and 2.9mm (p value 0.0001) after 3 months and 6 months respectively and in secretory endometrium from 11.1 to 2.1mm (p value 0.0005) and 1.9mm (p value 0.0003) after 3 and 6 months respectively.

In our study we have analyzed the efficacy of ormeloxifene in patients with dysfunctional uterine bleeding and our results suggested that there was a significant reduction of menstrual blood loss, these results are similar to other studies. Ormeloxifene's effect on hemoglobin was examined in our study, and the results showed a considerable increase in hemoglobin levels (18.35% in 3 months and 27.26% in 6 months). Ravibabu et al. also reported a rise in hemoglobin from 9.2 to 10.5 gm/ml in 6 months. In six months, the mean hemoglobin increased from 10.6 gm/ml to 11.2 gm/ml, according to Kriplani et al and other studies.[12,13] A study by Ravibabu et al found that 84% of patients had relief from dysmenorrhoea ($p<0.001$) whereas no such findings were recorded in our study.[11]

The PBAC score decreased as a result of the ormeloxifene effect in our study; the decline was 41.39% in 3 months and 61.06% in 6 months. However, Shravage et al. discovered that the mean PBAC score decreased by 85.71%,

which was a greater reduction than our study.[14] Comparable to our investigation, the study by Chhatrala et al. found that the PBAC score decreased by 56.9% over the course of six months while taking ormeloxifene.[15] Presence of clots, an obvious evidence of excessive menstrual flow, was maximally reduced in the ormeloxifene group. The results of the present study are comparable to the study by Biswas et al.[16]

5. Conclusion

Ormeloxifene may be the medication of choice for individuals with HMB based on these findings because it is extremely safe, reasonably priced, and has tolerable side effects. This straightforward medication-based therapy has improved patient compliance, tolerability, and treatment adherence due to a discernible decrease in symptoms. Additionally, it lowers the risk of breast cancer because of its anti-estrogen impact on breast tissue. It is particularly a better option for patients who are at high risk of surgery, young women who want to use contraception, and perimenopausal women to get through that time and embrace amenorrhea.

Among all the conservative methods for the medical management of menorrhagia, one of the most effective and safest medications is ormeloxifene. Surgical treatments are the last resort in the event that medical care, which has always been the first therapeutic alternative considered, is ineffective. Thus may be regarded as the initial course of treatment for HMB patients.

6. Source of Funding

No funding resources.

7. Conflict of Interest

None declared.

8. Ethical Approval

Ethical No.: 92 IEC/ACPMMC/Dhule.

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