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Original Research Article

Efficacy and safety of ormeloxifene, a selective estrogen receptor modulator in management of dysfunctional uterine bleeding in perimenopausal patients: a prospective interventional study

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ABSTRACT

Background: Dysfunctional uterine bleeding (DUB) is one of the most common menstrual disorder of women in any age group and is a diagnosis of exclusion. Medical management of menorrhagia is a difficult task as there are wide variations in the available drugs and a lot of different regimes are available. Present study evaluates efficacy and safety of ormeloxifene a selective estrogen receptor modulator (SERMs) in treatment of dysfunctional uterine bleeding in perimenopausal women.
Methods: The study was conducted on 120 patients in the age group of 40-55 years who were treated with 60 mg ormeloxifene twice a week for first 12 weeks and once weekly for next 12 weeks. The primary outcome measures were menstrual blood loss (assessed by pictorial blood assessment chart score), hemoglobin concentration and endometrial thickness. The secondary outcome measures were aceptability and side effects of ormeloxifene.
Results: 86.66% of women showed marked improvement in symptoms. Mean endometrial thickness decreased significantly from 9.825 mm to 6.25 mm after 6 months of treatment (p value <0.001). A significant decrease in median PBAC score (p value <0.001) was observed. Also, the mean haemoglobin level increased significantly from 8.03 g/dl to 9.60 g/dl (p value <0.001). Most common side effect reported was amenorrhoea (16%). 4% patient not relieved underwent hysterectomy.
Conclusions: Ormeloxifene could be the drug of choice in patients with DUB. It is safe, cost-effective with manageable side effects. The therapy has facilitated compliance, tolerability and reduction of symptoms resulting in adherence towards the treatment.

Keywords: Ormeloxifene, Dysfunctional uterine bleeding, PBAC, Selective estrogen receptor modulator

INTRODUCTION

Dysfunctional uterine bleeding is defined as variation in regularity, frequency, duration and amount of blood loss from the normal menstrual cycle.[1] It is without any clinically detectable organic, systemic and iatrogenic cause, and is a diagnosis of exclusion. It is one of the most common menstrual disorder of women and its prevalence ranges between 10-30% worldwide.[2] It can affect any woman from menarche to menopause, but is more common in extreme age group.[3,4] This is the most common cause of iron deficiency anaemia in healthy fertile women.[5] Untreated long anovulatory cycle may result in hyperplasia and endometrial cancer.[6] Wide range of treatment modalities are available which include both medical and surgical modalities. However, surgical treatment is often resorted in case of failure of medical management. The available medical treatment options are oral or intramuscular progesterone, levonorgestrel intrauterine system (LNG-IUS), anti-fibrinolytic agents like tranexamic acid, gonadotropins releasing hormone, and combined oral contraceptives pills. However, each

medications has its own disadvantages. Prolonged use of daily oral contraceptives has problems like poor compliance and the risk of side effects like the life-threatening thromboembolism.[1,7] Role of LNG-IUS in AUB is now well established and is considered to be the foremost option in medical management, but its high cost limits its ubiquitous use.[8]

Ormeloxifene is a third-generation selective estrogen receptor modulator (SERM). It is a non-steroidal, non-hormonal oral contraceptive, which is available as a birth control pill, by the name of SAHELI since 1990s.[9]

It is having anti-estrogenic action on uterine and breast tissue, hence does not increase the risk of endometrial and uterine cancer. However, it is having estrogenic effect on vagina, bone, cardiovascular and central nervous system, and hence prevents vaginal dryness, bone loss, lowers cholesterol level, making it especially beneficial in perimenopausal women.[9,10] Thus, it has the additional advantage of reducing premenstrual symptoms, mastalgia and dysmenorrhea. Unlike progesterone, ormeloxifene does not produce spotting, breakthrough bleeding or menorrhagia.[11] The effect of this SERM on the vascular endothelium leads to decrease in blood loss and thereby amelioration of symptoms in dysfunctional uterine bleeding. It is given in a dose of 60 mg twice weekly for 12 weeks followed by weekly for next 12 weeks. The drug is metabolized in liver and has a half-life of 170 hours. Highest concentration of drug is seen in uterus next only to liver.

Common contraindications are hepatic dysfunction, pregnancy, lactation, chronic illness, PCOS. Common side effects are nausea, vomiting, weight gain and delayed menstruation.[5] Ormeloxifene have longest safety margin, and the cost of treatment is also comparatively less.[5] It is licensed under the name of Novex-DS, Centchroman and Sevista.

With this view, the study was conducted to find out efficacy and safety of ormeloxifene in treatment of dysfunctional uterine bleeding in women of perimenopausal age group.

METHODS

This is a hospital-based prospective study in which consecutive patients of perimenopausal age group (40-55 years) having DUB, attending the gynecology outdoor patient department in our referral hospital were included. Patients signing the informed consent form were evaluated for eligibility.

Inclusion criteria

All women of perimenopausal age group (40-55 years) with DUB excluding all structural and functional causes of abnormal uterine bleeding and those willing to give informed consent were included in the study.

Exclusion criteria

Women with pelvic pathologies like uterine fibroids, adenomyosis and ovarian tumors; having malignancies of uterus/cervix/ovary/vagina/endometrial hyperplasia with atypia; having medical diseases like-liver dysfunction, heart disease, migraines, stroke, renal disease, hypo/hyperthyroidism, platelet disorders or coagulopathy, previous history of thrombosis; women who have pregnancy, recent abortion, using IUCDs or oral contraceptives or those who are lactating in first 6 months of post-natal period and those having hypersensitivity to ormeloxifene were excluded from the study.

Data collection

Total 120 patients meeting our inclusion criteria were enrolled. The study protocols were approved by institutional ethics committee. It was carried out between October 2017 to June 2019. Patients attending outpatient department of obstetrics and gynaecology with heavy menstrual bleeding (HMB) from October 2017 to June 2019 -were included in the study. The participants were explained about the study and were assured that their identity would be kept confidential. Pts were given the option to refuse participation in the study. Written and informed consent was obtained from the study participants prior to the interview.

Details like age, medical, obstetric and menstrual history were documented. General examination, per abdomen and bimanual examinations were performed. The menstrual blood loss was assessed by pictorial blood assessment chart (PBAC). All routine investigations like Complete blood count (CBC), blood grouping and typing were done. Transvaginal ultrasound was done to measure endometrial thickness, and to rule-out any pelvic pathology. All included cases were treated with ormeloxifene 60 mg orally twice a week for 12 weeks, followed by once a week for another 12 weeks. Patients were asked to maintain menstrual calendar. Patients were called at monthly interval. At each visit, a detailed menstrual history was taken and physical examination was done. Menstrual blood loss was measured objectively by PBAC score as described by Higham et al (Table 1).[13] PBAC is a simple and less time-consuming procedure for objective assessment of menstrual blood loss. A PBAC score >100 indicate a menstrual blood loss >80 ml and is considered diagnostic for menorrhagia.[13] After 6 months of treatment, haemoglobin and transvaginal ultrasound and endometrial sampling were repeated, and pre-treatment values were compared to that of post-treatment values.

Statistical analysis

All data are entered in a Microsoft excel sheet and statistical analysis was made by statistical package for the social sciences (SPSS) version 23. Descriptive statistics and paired T test were used to analyze the data. P value less than 0.05 is considered significant.

Table 1: PBAC scoring system.

Variables	PBAC score
PADS	
Lightly soiled	1
Moderately soiled	5
Saturated	20
CLOTS	
Small (smaller than a rupee coin)	1
Large (large than rupee coin)	5

RESULTS

Of total 120 included patients, 65% were in the age range of 40 to 45 years and 35% of the patients were between 46 to 55 years of age group. The mean age among the study participants was found to be 47.2±2.7 years. Regarding the parity 52% of the women had two children while 42% of the study women had three children. Parity status was four and five among 3% of the women each. Table 2 is showing the clinical profile of patients. Based on the days of menstrual cycle for 60% of the peri menopausal women, the flow was less than or equal to 10 days and for 40% of the women had more than 10 days flow in a cycle. The mean flow days in a menstrual cycle among the study cases were recorded to be 11.3±3.5 days/cycle. Menstrual cycle length was less than 35 days for 85.5% of the cases and more than 35 days for 14.5% of the cases in this present study.

Table 2: Clinical profile of patients.

S. no.	Clinical parameter	Mean
1	Age	47.2±2.7 (40-55)
2	Parity	3 (1-6)
3	Duration of menses	11.3±3.5 days/ cycle

Menstrual blood loss was assessed by PBAC and calculated at beginning and then at 6 months of treatment. The median pretreatment PBAC score was 309 and reduced to 57.5 at six months of therapy ($p<0.001$). Due to skewing of data (some extreme value), we also calculated median value in PBAC scoring (Table 3). The mean hemoglobin of the patients at the start of treatment was 8.03 g/dl. After six months, the mean HB was 9.60 g/dl. There was a significant increase in mean HB concentration with a rise of 1.57 g/dl after 6 months of therapy with ormeloxifene ($p<0.001$). Table 3 is showing the outcome measures of study after 6 months of therapy.

Table 3: Outcome measure of the study after 6 months.

Parameter	Pre-treatment	Post-treatment	P value
PBAC: mean±SD	316.7±41.0586	63.9±50.98	<0.001
Range	214-410	15-254	
PBAC: median	309	57.5	<0.001
Hb level: mean±SD	8.03±1.151	9.60±1.02	<0.001
Range in gm/dl	6.1-11.4	6.80-12.5	
Endometrial thickness: mean±SD	9.825±2.549	6.25±1.785	<0.001
Range	5.0-14.5	3.0-9.5	

Patients were asked about the subjective improvement in their symptoms of DUB. 86.66% of patients (104 out of 120) showed marked improvement in symptoms. 4 patients had no improvement and 10 patients had mild improvement. Only 2 patient had an aggravation of symptoms during the therapy. 8 out of 60 patients (6.66%) underwent hysterectomy (Table 4).

Table 4: Subjective assessment of symptoms.

Subject	Improvement number	Percentage
No improvement	4	3.33
Mild improvement	10	8.33
Marked improvement	104	86.66
Aggravation of symptoms	2	1.66
Total	120	100

There was no major side effect with the therapy. Most common complaint was amenorrhoea which was seen in 20 patients (16%). Hypomenorrhoea was reported in 6 patients (5%). Gastric irritation, headache, abdominal pain were other symptoms reported but were not significant.

DISCUSSION

Menorrhagia accounts for most of the referrals to gynaecological OPD and in majority of cases, no organic pathology is found. DUB is a diagnosis of exclusion. It occurs more commonly in the first 5 years after a woman starts menstruating and as she approaches menopause, but it can occur at any age. For women with DUB who wish to retain fertility, pharmacological approaches are the only currently available options. Among the other pharmacological agents, some are effective only for anovulatory DUB, some are useful only for ovulatory DUB, and still others may be effective for both. Pharmacological agents such as NSAIDS, oral contraceptive pills, progestins, danazol, GnRH agonists

and antifibrinolytic drugs all reduce menstrual blood loss; however, the assets are limited to the duration of treatment.

Selective estrogen receptor modulators are drugs that act in specific ways at each of the estrogen receptor site in different tissues.[13] Ormeloxifene is an optimally designed SERM with varied tissue response. It is indicated for the treatment of dysfunctional uterine bleeding at any age. It offers the additional advantage of relief of premenstrual syndrome in peri-menopausal women. Compliance to the drug is also good due to convenient dose regimen. Also, the medication is cost-effective. However, it is not suitable for women desiring pregnancy in view of its contraceptive property.

The present study was conducted to evaluate the efficacy and safety of ormeloxifene in the management of DUB in perimenpausal women. The study showed that there was a significant reduction in menstrual blood loss with ormeloxifene, as assessed by fall in PBAC score and improvement in patient's subjective symptoms. The median PBAC score decreased from 309 to 57.5 after 6 months of treatment which is statistically significant ($p<0.001$). The findings were similar to study by Kriplani et al in which median PBAC score significantly reduced from 338 to 5 after 4 months of therapy.[12] Similarity, mean PBAC score decreased from 354 to 40 at the end of 24 weeks of treatment in study by Sarabhai et al.[14]

The results of our study suggests that there was a significant rise in haemoglobin concentration from 8.03 to 9.6 g/dl after six months of treatment with a rise of 1.57 g/dl. The endometrial thickness decreased from 9.825 mm to 6.250 mm with 6 months therapy of ormeloxifene which was statistically significant, and was comparable to different studies as shown in Table 5.

Table 5: Comparison of study parameters among different studies post-treatment.

Author	Year	Difference in median PBAC	Rise in hemoglobin level (g/dl)	Decrease in endometrial thickness (mm)	P value
Biswas et al[15]	2004	97.2	1.3	1.2	<0.05
Dadhich et al[4]	2012	364	2.8	4.94	<0.05
Dhananjay et al[16]	2013	-	2.33	3.47	<0.05
Sarabhai et al[14]	2023	314	1.45	2.24	<0.05
Present study		251.50	1.57	2.575	<0.05

Our study showed a significant improvement of patient's condition both subjectively and objectively. 88.33 % of patients showed marked improvement of symptoms, which was comparable to study by Bhattacharyya et al, Dadhich et al and Agarwal et al which showed marked improvement in 81.6%, 92% and 88.33% of patients respectively (Table 6).[4,8,17]

Table 6: Comparison of symptomatic improvement post treatment treatment with ormeloxifene among different studies.

Study	Year	Marked improvement in symptoms (%)
Bhattacharyya et al[18]	2010	81.67
Dadhich et al[4]	2012	92
Agarwal et al[17]	2013	88.33
Present study		86.66

Ormeloxifene was very well tolerated and practically there was no undesirable side effects. Amenorrhoea was the most common side effect seen in 8 patients (16%). Amenorrhoea was a common symptom seen in different studies with a wide range of 8% to 42.9%.[4,15,17] The strength of the study is its larger sample size and prospective nature of study. However, the follow-up of patients was only 6 months. Larger follow-up is needed to look for long term complications and any recurrence of symptoms. Also, larger randomized trials should be conducted to compare efficacy with other available medical therapies.

CONCLUSION

Based on these results we could conclude that ormeloxifene could be the drug of choice in patients with DUB as it is very safe, cost-effective with manageable side effects. This simple drug-based therapy has facilitated compliance, tolerability and noticeable reduction of symptoms resulting in adherence towards the treatment. Also, due to anti-estrogen action on breast tissue, it decreases the chances of breast carcinoma. It is especially a more suitable choice in perimenopausal women to tide over that period and in whom amenorrhea is welcomed, in patients who are at high risk of surgery, and also in young women who desire contraception.

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