ORIGINAL ARTICLE

Ormeloxifene – Looking beyond contraception

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ABSTRACT

Aims: This study is aimed at finding out a logical solution for perimenopausal menorrhagia in normal or bulky uterus.
Settings and Design: The study is carried out at a tertiary care hospital at Odisha. In our setup, nearly 900 hysterectomies are done per year out of which 60% are for menorrhagia with bulky uterus.
Subjects and Methods: There were sixty cases of menorrhagia between the ages of 40 and 55 years who completed child bearing treated with ormeloxifene. Their endometrial thickness (ET) and hemoglobin (Hb) level were determined at the start of the study and also at 6 months and compared. At 1 year from the start of treatment, patients' satisfaction and status of menstrual cycle were reassessed.
Statistical Analysis Used: Age and parity variables were expressed as mean ± standard deviation and range. We used the paired samples *t*-test to estimate the mean, median, range, *P* and *t* value. All statistical analyses were performed using SPSS software version 11.5 (IBM Corp) and tests of statistical significance were two-sided and differences were taken as significant when $P < 0.05$.
Results: After 1 year of follow-up, 90% of patients found to be amenorrhoic and only two out of them presented with mild irritability and vasomotor complaints which resolved with counseling and placebo therapy. There was a significant reduction ($P < 0.0001$) in ET and rise in Hb level ($P < 0.0001$).
Conclusions: Ormeloxifene is a safe drug which can be used to treatment of perimenopausal bleeding with minimal focal pathology.

Key Words: Hysterectomy, menorrhagia, ormeloxifene, selective estrogen receptor modulator

INTRODUCTION

Uterus is the epitome of womanhood. Abnormal uterine bleeding (AUB) can affect 1/3rd of women of child bearing age and is one of the most common gynecological symptoms encountered in day to day basis.[1] The wide spectrum of disturbance in AUB leads to remarkable social and physical morbidity in all societies and may also reflect a serious underlying pathology. Menorrhagia affects 10%–30% of menstruating women at any 1 time and may occur in perimenopausal transit phase in up to 50% of women.[1-3] Studies have shown that mean menstrual blood loss is 60–80 ml per month and associated with iron deficiency anemia. AUB involves any disturbance in regularity, frequency, duration, or volume of menstrual flow and the cause may be physiological, pathological, or pharmacological.[4,5]

Although there has been escalation in the efforts to find a less invasive surgical approach such as endometrial ablation, still hysterectomy remains as the only suitable definitive therapy for those who have no further fertility concerns. The demand for alternative to surgery for reducing menstrual blood loss continues. To avoid the morbidity

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associated with hysterectomy, RCOG recommends beginning treatment with medical management before resorting to surgical interventions.[6]

To manage the menorrhagia by medical methods is indeed a very challenging task in a scenario where there is lack of consensus for the drugs to be prescribed in such a condition. The wide variations in drugs used for treatment of AUB include nonsteroidal anti-inflammatory drugs, antifibrinolytics, combined estrogen and progesterone or progesterone alone, high-dose estrogen, gonadotropin-releasing hormone (GnRH) agonists, danazol, and levonorgestrel-releasing intrauterine system. Although effective in reducing blood loss, their main drawbacks are their costs and adverse effects when used for long period.

Ormeloxifene is the latest designer drug available for treatment of AUB. It is a 3rd generation selective estrogen receptor (ER) modulator that have high affinity to the ERs and act like estrogens in some tissues such as vagina, bone, cardiovascular, and central nervous system and have antiestrogenic effect in uterus and breast.[7] This forms the basis for its pharmacological role in AUB. The identification of two types of ER α and ER β and the knowledge about the complexity of ER structure and functions give a major therapeutic opportunity of finding a compound with beneficial bone, cardiovascular, and neurological profile without adverse effect on reproductive tissues of uterus and breast. The selective ER modulation is based on the existence of two receptor isoforms of different ligand affinity coexisting in many tissues, the existence of at least 2 activating factors, and the increasing number of coactivators and corepressors.

Ormeloxifene is best known as a nonhormonal, nonsteroidal oral contraceptive taken once a week. Available since the 1990s, it is marketed as centchroman.[8] When it was used as a contraceptive, there was improvement in menorrhagia and endometriosis, which led to control trials for the management of menorrhagia after its approval for this indication. In addition, it also reduced premenstrual symptoms, mastalgia, and dysmenorrhea by regularizing expression of ERs on the endometrium it normalizes the bleeding from uterine cavity.

The chemical name of ormeloxifene is trans-7-methoxy-2, 2-dimethyl-3-phenyl-4 (4-(2-pyrrolidinoethoxy) phenyl (-chromanhydrochloride).[9] Ormeloxifene competitively binds with cytosol receptors and not only blocks them but also cause prolonged depletion, so that its action lasts longer even after withdrawal of drug. It is well absorbed from the GI tract, attains a peak level in 4 h, and its terminal half-life is 170 h. It has little affinity to plasma proteins.

The hypothesis of the present study is that the ormeloxifene will effectively reduce menorrhagia by causing thinning of endometrium and hence will improve the physical condition of the patient. This prospective study of 2 years duration was taken up in a tertiary hospital of Odisha, to observe the efficacy and safety of the drug.

SUBJECTS AND METHODS

In our setup, nearly 900 hysterectomies are done per year out of which 60% are for menorrhagia with bulky uterus. This study was planned to determine the effect and safety of ormeloxifene in the treatment of menorrhagia and hence to reduce the number of hysterectomies. A detailed case record form was developed. Perimenopausal women of 40–60 years of age with complain of menorrhagia (cyclical/acyclical) were included in the study. Patients with uterine size 12 weeks or more (i.e., abdominally palpable uterus) adnexal mass, active heavy bleeding necessitating hospitalization, breast or genital tract malignancy, bleeding due to pregnancy complication, women with evidence of hepatic, renal, cardiac, or metabolic disorder were excluded from the study.

An institutional ethical clearance for the study was taken. An informed consent was taken from the women who were selected for the study. History of the patient was recorded in proper pro forma. All were investigated to rule out associated systemic and metabolic disorder. A pretreatment hemoglobin (Hb) level and endometrial thickness (ET) were recorded. All were given ormeloxifene 60 mg twice weekly for 12 weeks and then once weekly for 12 weeks. At the end of 6 months, all were reevaluated and estimation of ET and Hb level done. All the patients were followed up till completed 1 year following end of treatment to assess their clinical status.

RESULTS

In the present study, 60 patients with perimenopausal menorrhagia were treated with ormeloxifene for 6 months. Two patients out of sixty had to undergo hysterectomy due to deterioration of symptoms and excluded from analysis. Demography of all 60 patients is depicted in Table 1. The age of the patients varied from 42 to 54 years with mean of 46.28 years. Muliparous and primipara patients found 76.7% and 23.3%, respectively, from the studied 60 number of patients. In the study group, 8 patients had adenomyosis, 28 AUB, 4 endometriosis, and 20 patients were diagnosed with small intramural fibroids. After follow-up of 1 year, it was revealed that 54 attained amenorrhea. Improvement in terms of rise in Hb and decreased ET marked in 56 patients. There was mean rise of Hb level from 9.76 g%

at commencement of treatment to 11.07 g% at 6th month of treatment. Significant decrease in mean ET noticed from 8.569 mm to 3.628 mm at 6 months of treatment. We compared the level of ET and Hb with *t*-test and found that the improvement was statistically significant in terms of rise of Hb level as well as decrease in ET after use of the drug at $P \leq 0.0001$ [Table 2]. This shows that ormeloxifene is a significantly effective drug which can be used in the management of perimenopausal menorrhagia even with certain uterine pathologies such as mild adenomyosis, small fibroadenomas, and Grade I endometriosis where the uterus is not more than 12 weeks size. The same analysis when applied to patients with different age group yields no significance [Table 3]. Hence, we concluded that the drug ormeloxifene is equally effective in the management of perimenopausal women in 40–55 years of age. Out of six patients who did not have amenorrhea, four became hypomenorrhoic (6.67%) and two patients had worsening of symptoms in terms of menorrhagia, eventually deciding for hysterectomy were considered as treatment failure (3.3%). Only two of the amenorrhoic patients had postmenopausal vasomotor symptoms [Table 4]. In the present study, it has been seen that 90% of patients attained menopause at 1 year of time. This shows that the drug has minimal side effects and it does not cause any aggravation of postmenopausal symptoms.

Table 1: Demographic characteristics of study group

Parameter	Frequency
n	58
Mean age (years)	46.28
Parity	
Multipara	44
Primipara	14
Adenomyosis	8
AUB	26
Endometriosis	4
Fibroid	20

AUB: Abnormal uterine bleeding

Table 2: Evaluation of treatment based on hemoglobin level and endometrial thickness

Statistical parameter	Hb level (g/dl)		ET (mm)	
	At 0 month	At 6 months	At 0 month	At 6 months
Mean	9.766	11.072	8.569	3.628
SD	0.628	0.698	2.223	1.056
SEM	0.082	0.092	0.292	0.139
n	58	58	58	58

SD: Standard deviation, SEM: Standard error of mean, Hb: Hemoglobin, ET: Endometrial thickness

DISCUSSION

The main aim of the study is to manage menorrhagia, avoid risk of hysterectomy, and to improve the quality of life of the patients. Menorrhagia is usually a loss of menstrual blood which leads to physically incapacitating condition, socially embarrassing, and has great financial drain.[10] The study validates the use of ormeloxifene drug for its easy administration with minimal risk and side effects. The results suggested that there is a significant increase in Hb level ($P < 0.0001$) and decrease in ET ($P < 0.0001$) as because ormeloxifene has anti-proliferative effect on endometrium which causes endometrial atrophy leading to decrease in menstrual blood loss. Our study is in accordance with Bs and Nanda[11] and also with Kriplani *et al.*,[9] where they have found a significant rise in Hb level and decrease in ET. Grover *et al.*[12] have also shown in their study that there was mean increase of Hb by 0.42 g%. Mechanism behind improvement of Hb level and menorrhagia may be due to antagonistic effect of ormeloxifene on endometrial ER which enhance prolong depletion of estrogen due to decrease in receptor stimulation.[1,13] Other drugs used for management of AUB are progesterone,[14] danazole, GnRH analog out of which danazole are rarely used because of its side effects whereas GnRH analog is much costly and also associated with increase occurrence of vasomotor symptoms and osteoporosis.[15] Progesterone is the most commonly used compound which gives rise to irregular acyclical spotting on long-term use though it has good cycle control, the symptoms recur after stoppage of drug.

A study by Agarwal and Singh[16] has also demonstrated mean increase in Hb concentration and a significant decrease in ET by 6 months treatment with ormeloxifene which was found to be a very safe drug as there was no major problem encountered by the patients during their treatment period. Biswas *et al.* also reported average increase of 1.31 g/dl in Hb concentration in Indian population.[17]

Table 3: Role of ormeloxifen on endometrial thickness and rise of hemoglobin in different age group

Age group	Mean ET		Mean difference	Mean Hb		Mean difference
	At 0 month	At 6 months		At 0 month	At 6 months	
40-45	8.18	3.35	4.83	9.63	10.78	1.15
46-50	8.49	3.63	4.86	9.77	11.25	1.48
51-55	9.68	4.26	5.42	10.16	11.42	1.26

Hb: Hemoglobin, ET: Endometrial thickness

Table 4: Subjective assessment of symptoms

Serial number	Subjective improvement	*n*	Percentage
1	No improvement	0	0.00
2	Mild improvement (hypomenorrhea)	4	6.90
3	Marked improvement (amenorrhea)	54	90.00
4	Aggravation of symptom (amenorrhea)	2	3.45
Total		58 (serial number 4 is excluded because of hysterectomy)	100

Moreover, incidence of postmenopausal symptoms was minimal with use of ormeloxifene.

CONCLUSIONS

Ormeloxifene is a novel compound which can be used in the management of AUB where uterus size is not very big. It can avoid many hysterectomies. Long-term study and meta-analysis will prove its safety and efficacy. The drug is equally effective in perimenopausal women of all age group.

Limitation of the study

This study is conducted over a small sample and also study period is very less. It needs a follow-up over a long-time period to conclusively decide about efficacy of the drug.

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Conflicts of interest

There are no conflicts of interest.

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