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Ormeloxifene in Menorrhagia: An Experience

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Abstract: *Abnormal uterine bleeding is one of the common gynecological problems women face and causing a serious threat to health as well as a great economic burden.*
Aim: The study aims to assess the efficacy of selective estrogen receptor modulatory action of Ormeloxilene in the treatment of menorrhagia.
Subjects and methods The study was conducted at hospitals in Northern India from 01 January to 31 Aug 2015 on 50 patients with menorrhagia. The patients diagnosed as DUB and IUCD induced menorrhagia and perimenopausal menorrhagia were included in the study. The patients with menorrhagia for the sake of convenience had been grouped into four clinical patterns: normal cycle, prolong cycle, short cycle, and irregular cycle. The dose of a schedule of ormeloxifene followed was 120mg tablet twice weekly for twelve weeks followed by 60mg twice weekly, starting at the time of menstruation. The results were evaluated statistically.
Result Menorrhagic patients were seen 10% in 20-25 years, 16% in 26-30 years, 20% in 31- 35 years, 32% in 36-40 years and 20% 41 and above of age. . The menstrual pattern observed was a regular cycle 60%, irregular cycle in 18%, short cycle in 12% and long cycle in 10%. Overall 78% of patients had relief from menorrhagia and 76% had relief of dysmenorrhea.
Conclusion The Ormeloxifene is found to be effective in the management of dysfunctional uterine bleeding especially in menorrhagia with short cycles and is perimenopausal age group. The greatest advantage is its absence of progestational and other side effects of conventional hormonal preparations and is available at a nominal price. In the future, it may be used in several other indications more frequently.

Keywords: *Menorrhagia, DUB, SERM, Ormeloxifene,*

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I. Introduction

Abnormal uterine bleeding is one of the commonest gynecological problems women face and causing a serious threat to health as well as great economic burden. There are several medical and surgical means for the management of the disease. The pharmacological options are limited and poor compliance of the patient due to adverse effects and inefficacy is a hindrance. Newer pharmacological agents are in constant search for effective management of the condition. The discovery that pharmacological agents can be estrogenic in some tissue while anti-estrogenic in others has led to an interest in better understanding the mechanism by which molecular structure interacts with the cellular receptors to selectively affect DNA transcription in different organs. Selective estrogen receptor modulators are a new category of therapeutic agents that bind with high affinity to estrogen receptors and mimic the effect of estrogen in some tissues but acts as anti-estrogens in others. The new selective estrogen receptor modulator drugs popular known as designer estrogen are being developed to find a treatment that will stimulate bone and cardiovascular tissue the way estrogen does while not stimulating breast and uterine tissue. The loss of reproductive actions on bone, brain, vascular tree,gut, immune system which may confer significant disadvantages. Replacement of estrogen is a safe and efficacious incompetent hand but is attended by the resurrection of estrogen acceptance of hormone replacement therapy (HRT) (1, 2). Such effects, which are clinically apparent as cyclic or unscheduled bleeding and as a small but significant increase in breast cancer risk,(3) deter many women from considering the continuation of conventional HRT preparation. Moreover, concern has been expressed that endometrial cancer may not be fully prevented by progestogen. (4)

The recent burgeoning of understanding of estrogen receptor(ER) structure and function has allowed the development of agents which like estrone and estradiol engages the ER but which selectively rather than generally, deliver estrogen agonism where required and antagonism where necessary. The ER is not a single entity, nor is it confined to the reproductive system. Two receptors are known, styled ER Alpha and ER Beta

and there is evidence that there may be others. (5) The development of selective estrogen receptor modulators (SERMs) thus parallels the earlier development of selective B-adrenergic, histamine (H2) and COX2 antagonists, which has advanced the management of coronary artery disease, peptic ulceration, and osteoarthritis. The development of the SERMs was born out of the meticulous recording of scientific detail and clinical effect, long before the complexities of ER were unraveled. The triphenylethylene agent tamoxifen and clomiphene are first-generation SERMs Raloxifene is the first second-generation and Ormeloxifene is a third-generation SERM to have been launched commercially. Increasing knowledge of ER function will enable the development of SERM suitable for women of reproductive age, and thus could be of value in case of endometriosis,leomyoma, dysfunctional uterine bleeding, and mastalgia. (6)

The development of Ormeloxifene a SERM which selectively functions as an estrogen antagonist in reproductive tissues. It not only blocks estrogen receptors but also causes their prolonged depletion and therefore its action lasts longer than conventional antagonists do. It does not affect the liver, kidneys, blood pressure and behavior. It is the only anti-implantation agent approved for clinical use in the world. It has a large safety margin. It does not affect the hypothalamic-pituitary-ovarian functions, hence E2. Progesterone, FSH, LH levels are not altered during the treatment. Ormeloxifene does not posses progestational, androgenic or anti-androgenic properties; likewise, it does not affect the secretions of pituitary, thyroid or adrenaline hormones in the usual therapeutic doses. No abnormal or deleterious effect on the secretions of pituitary, thyroid or adrenaline hormones in the usual therapeutic doses. No abnormal or deleterious effect of ormeloxifene on any of the body systems was observed during its trial as oral non-hormonal contraceptives. (7)

Clinical pharmacology

The chemical name of ormeloxifene is Trans-7-methoxy-2,2,-dimethyl-3-phenyl-4 ,phenyl -4.Ormeloxifene is white to off-white powder, having m p of 163 degrees Celsius to 166 degrees Celsius and mol. Wt of 493.5. It is very stable under normal conditions of storage and suitable assay methods have been standardized. After administration of a single 60mg oral dose of Ormeloxifene, the concentration of the drug in serum at 30 minutes raised 63ng/ml and a peak of 125ng/ml was achieved in 4 hours. The terminal disposition half-life of the drug was calculated to be about 170 hours.

II. Aim

The study aims to assess the efficacy of selective estrogen receptor modulatory action of Ormeloxilene in the treatment of menorrhagia.

III. Subjects and methods

A detailed protocol and case record form was developed for the study of menorrhagia. The patients diagnosed as DUB and IUCD induced menorrhagia and perimenopausal menorrhagia were included in the study. Patients with the uterine size more than eight weeks, adnexal mass or tenderness, active heavy vaginal bleeding necessitating emergency treatment, breast or genital tract neoplasia, bleeding due to pregnancy compilation such as incomplete abortion, vesicular mole, women with any evidence of hepatic, renal, cardiac, metabolic dysfunction and active tuberculosis were excluded from the study.

The patients between 20 and 45 years of age were accepted for the study. The study was conducted at hospitals in Northern India from 01 January to 31 Aug 2017. Ormeloxifene used was in the form of 'Sevista' (Ormeloxifene Hydrochloride tablets I.P 60mg, manufactured by Torrent Pharmaceuticals Ltd. The dose schedule followed was 120mg tablet twice weekly for twelve weeks followed by 60mg twice weekly, starting at the time of menstruation. The total duration of treatment was titrated with the improvement of symptoms. The patients who did not respond adequately was further evaluated by ultrasonography and endometrial biopsy.

A detailed history, systemic examination, gynecological examination, and hemoglobin level estimation was carried out and consent was obtained after explaining the nature of medication and its adverse effects. Subsequently, patients were reviewed, after menstruation any intermenstrual bleeding or any other symptoms. A detailed inquiry into a menstrual pattern, breast symptoms, and systematic and pelvic examination were carried out. Medications were provided free of cost to each patient for a month at each monthly visit. The results were statistically evaluated by an appropriate method for inference.

A total of 50 patients with menorrhagia were selected for the study. The patients with menorrhagia for the sake of convenience had been grouped into four clinical patterns:

Normal Cycle
Prolong Cycle
Short Cycle
Irregular Cycle

IV. Observation

Menorrhagia patients were seen 10% in 20-25 years, 16% in 26-30 years, 20% in 31- 35 years, 32% in 36-40 years and 20% 41 and above of age. Table-1

Table 1
Age of patients

Menstrual pattern	no	%	(20-25)yrs		(26-30) yrs		(31-35)yrs		(36-40)yrs		(41-45)yrs	
				%		%		%		%		%
Regular	30	60	3	10	4	13	6	20	9	30	8	26
Irregular	09	18	0		1	11	2	22	4	44	1	11
Short	06	12	0		2	33	1	16.6	2	33	1	16.6
Long	05	10	2	40	1	20	1	20	1	20	0	
Sub Total	50		5	10	8	16	10	20	16	32	10	20

Eighteen percent of patients with menorrhagia were constituted by nulliparae, 18% primipara, 32% second para, 22% by the third para and 10% fourth para and above. The menstrual pattern observed was a regular cycle 60%, irregular cycle in 18%, short cycle in 12% and long cycle in 10%. Of the menorrhagia patients, 60% had a regular cycle,18% had an irregular cycle,12% short cycle and 10% had a long cycle respectively. (Table -2)

Table 2
Parity

Menstrual pattern	No	%	0		1		2		3		4 & above	
				%		%		%		%		%
Regular	30	60	3	10	7	23	10	33	6	20	4	13
Irregular	09	18	4	44.4	0	0	2	22	2	22	1	11
Short	06	12	0	0	2	33	3	50	1	17	0	0
Long	05	10	2	40	0	0	1	20	2	40	0	0
Total	50		9	18	9	18	16	32	11	22	5	10

The response of ormeloxefine to the menorrhagia women was variable and gradual. Of the 30 patients with regular cycle 5(16.6%) after the first cycle, 8(26.6%) after the second cycle,10(33.3%) after the third cycle had relief and 7(23.3%)patients had no improvement. Of the 9 patients with an irregular cycle, none responded in the first cycle, and 3(33.3%) in a second and third cycle each had responded well but 3(33.3%) had no improvement. Of the 6 patients with a short cycle,1(16.6%)s in the first cycle,2(33.3%) in a second and third cycle each had relief and 1(16.6%) had no improvement. Of the 5 patients with a long cycle, none had responded on the first cycle,2(40%) each in the second and third cycle had relief and1(20%) had no improvement. Of the 50 menorrhagia patients,6(12.5%) in the first cycle,15(30%) in the second cycle,18(36%) in the third cycle had relief and 11(22%)patients did not experience any improvement. Overall 78% of patients had relief from menorrhagia. (Table no 3)

Table No. 3
Response to Ormeloxefine in Menorrhagia

Menstrual pattern	no.	%	1st cycle		2nd cycle		3rd cycle		No improvmnt	
				%		%		%		%
Regular	30	60	5	16.6	8	26.6	10	33.3	7	23.3
Irregular	09	18	0	0	3	33.3	3	33.3	3	33.3
Short	06	12	1	16.6	2	33.3	2	33.3	1	16.6
Long	05	10	0	0	2	40	2	40	1	20
Total	50		6	12	15	30	18	36	11	22

Other menstruation-related complaints such as dysmenorrhea were seen in 34(68%) and 25(73.6%) had achieved relief after the third cycle. Vaginal spotting was seen in 9(18%) patients of which,8 (88%) had relief after the third cycle. Passage of clots during menstruation was seen in 36(72%) patients of which 34(95%) had relief after the third cycle. (Table-4)

Table No. 4
Response to Ormeloxefine in other menstrual problems

Menstrual pattern	no		1st cycle		2nd cycle		3rd cycle		No improvement	
	No	%	No	%	No	%	No	%	No	%
Dysmen-orrhea	34	68	12	35	7	20.5	6	17.6	9	26.4
Spotting	9	18	3	33.3	3	33.3	2	22.2	1	11.11
Clots	36	72	18	50	9	25	7	19.4	2	5.5

No major adverse effect was noted in patients; headache in 6(12%) nausea and vomiting in 8(16%), abdominal pain and gaseous discomfort were seen in 5(10%) patients. These patients continued the treatment after adequate counseling. (Table-5)

Table no. 5
Adverse effect of ormeloxifene

Adverse feature	No. of patients	%
Headache	06	12
Nausea/Vomiting	08	16
Pain /discomfort in abdomen	05	10

The cost of medication is a very important factor in deciding the affordability and compliance of patients in a country like India. Commonly used in the treatment of menorrhagia such as norethisterone, duphastone, danazol are expensive compared to ormeloxefine which cost approx Rs 145 for a month course.(Table-6)

Table No. 6
Cost of drugs used in Menorrhagia per month

Name of the drug	Cost(Rupees)
Norethisteron	535
Duphostone	1700
Progesteron	743
Danazole	1736
Ormeloxifene	145

V. Discussion

Several gynecological diseases require hormonal manipulation for management and dysfunctional uterine bleeding is one of them. The Ormeloxifene with its unique estrogenic and anti-estrogenic activity-SERM like activity is found effective in these cases. The useful side effect of the drug is to bring menstrual bleeding late and occasional oligomenorrhoea can be utilized advantageously in menorrhagia with short cycles. In an interventional study on 99 patients of DUB treated with tablet ormeloxifene at a dose of 30 mg biweekly for 2 months followed by weekly for 4 months had resulted in the reduction of menstrual bleeding in 76% menorrhagia women of 36-40 years age. (8)

In a study of 1 year of follow-up, following ormeloxifene therapy,90% of patients found to be amenorrheic 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 ($P < 0.0001$). (9)

A study of 35 patients with DUB of age 40 years and above coming to were treated with 60 mg of Ormeloxifene was given twice a week for 3 months followed by weekly for 1 month. Patients were followed-up at 1, 3 and 4 months of therapy and then at 3 months after treatment stopped. Menstrual blood loss was measured objectively by the pictorial blood loss assessment chart (PBAC) score. The pretreatment median pictorial blood loss assessment chart (PBAC) score was 587 with a range of 186-893. After 4 months of treatment, mean PBAC scores reduced to 76.94±77.73 with a mean change of 490.05±155.4. It was statistically highly significant (P0.001). (10)

In a recent Indian study of 54 patients with dysfunctional uterine bleeding were treated with ormeloxifene for 3 months was given. Mean blood loss (MBL) was assessed using the pictorial blood loss assessment chart (PBAC), and subjectively by a visual analog scale (VAS). Ultrasonography (USG) for endometrial thickness and blood hemoglobin levels was done as a baseline and at 1, 3 and 6 months of treatment. The mean pretreatment MBL (PBAC score) was 343.13 (140-765), which reduced to 90.0 (0-340) at 3 months and 68.84 (0-320) end of 6 months. (11)

A population of 440 patients with dysfunctional uterine bleeding was divided into two groups –one was treated with MPA and another was treated with ormeloxifene. They were assessed for PBAC scores, endometrial thickness by USG, hemoglobin level and other side effects of the drug therapy. There was comparable efficacy in both groups and had a reduction of PBAC score by 755 and 79% respectively. (12)

In another study in a population consisted of 172 patients with dysfunctional uterine bleeding treated with ormiloxifene had reported of the median pretreatment baseline PBAC score found to be 317.00 with a range of 125-768. The median post-treatment PBAC score was 105.00 with a range of 3.0-557. The median decrease of 212 in the post-treatment PBAC score was statically significant. (13)

A study of a population of 100 patients with 68 patients was treated with centchroman in the premenopausal age group. Almost all the patients registered a rise in hemoglobin levels and an increase in the

duration of the length of cycle significant reduction of bleeding in 80% of the patients at the end of the study after treatment with centchroman. (14)

In 60 patients with DUB were grouped equally into A and B; treated with ormeloxifene and norethisterone respectively and were followed up at 1, 3 and 6 months. They were evaluated for menstrual blood loss assessed by PBAC score, rise in HB and TVS endometrial thickness assessment. There was marked improvement in hemoglobin level from 7.64 to 10 in Group A as compared to 8.8 in Group B. PBAC score also had a sharp reduction. Endometrial thickness reduced from 12.1 mm to 8.4 mm and 12.08 mm to 9.8 mm in Group A and B respectively at the end of 6 months. No major side effects were noted in either of the groups. (15)

In a study, conducted to evaluate the effect of ormeloxifene in patients with fibroid uterus and menorrhagia; no significant changes were observed in the size of uterine leiomyoma. In 90.9% cases, the fibroids remained unchanged, but the menstrual blood loss, PBAC score, and endometrial thickness had a statistically significant reduction, improvement of hemoglobin level and at the end of 6 months. The difference in mean hemoglobin concentration, PBAC scores, and endometrial thickness was statistically significant. (16)

Thirty patients with dysfunctional uterine bleeding were treated with ormeloxifene 60mg twice a week for 12 weeks and then once a week for 12 weeks. There was a significant reduction in mean PBAC score from 316 to 52 after six months of treatment. The mean hemoglobin concentration increased significantly from 8.4 to 9.8 gms/dl with a rise of 1.4gm/dl ($p < 0.05$). 76.7% of the women showed marked subjective improvement in symptoms. The most common side effect reported was amenorrhea (13.3%). (17)

In a prospective study in patients with AUB (L), the mean PBAC score was reduced by 81% with ormeloxifene (group I) compared with 43.8% for COC (group II). After 6 months,72% of patients in group I had PBAC scores in the non-menorrhagic range (<100) compared with only two (8%) in group II. Ormeloxifene with its simple low dosage schedule was effective in treating AUB-L, even though leiomyoma volume increased insignificantly with both ormeloxifene and COCs.(18)

In another study of 30 patients with DUB were given ormeloxifene 60mg twice a week for 12 weeks and then once a week for 12 weeks. There was a significant reduction in mean PBAC scores from 316 to 52 after six months of treatment. The mean hemoglobin concentration increased significantly from 8.4 to 9.8 gms/dl with a rise of 1.4gm/dl ($p < 0.05$). There was marked subjective improvement in symptoms 76.7% of the women and the common side effect reported was amenorrhea (13.3%). (19)

Conservative management of DUB, as well as fibroid uterus, is a preferred option compared to surgical options which have several disadvantages including premature menopause. An important factor in deciding the mode of therapy in the Indian context is cost and compliance, and Ormeloxifene is cheap with a monthly cost for treatment is only rupees one hundred forty-five. The big safety margin of doses, safety to lactating mother as well as the absence of mutagenic potential and freedom from hormonal adverse effects has made it appropriate therapy for use. The occurrence of abdominal pain, giddiness, and amenorrhoea has been mentioned in some studies. But in our study, we have observed giddiness, nausea, weakness and abdominal discomfort and pain in a few cases.

Ormeloxifene due to its positive bone metabolism effect and the protective cardiovascular effect is used in postmenopausal cases as prophylaxis. Ormeloxifene was found to be an excellent drug in controlling the symptoms of menorrhagia without affecting normal endocrinal and physiological parameters. The drug also has been approved for inclusion in the National Family Welfare program, Social Marketing of Health and Family Welfare of Government of India and is recommended for women of perimenopausal age groups. Recently under the aegis of CDRI Lucknow, Ormeloxifene has been evaluated for its efficacy in the management of breast cancer and osteoporosis.

VI. Conclusion

The Ormeloxifene is found to be effective in the management of dysfunctional uterine bleeding especially in menorrhagia with short cycle and is perimenopausal age group. The greatest advantage is its absence of progestational and other side effects of conventional hormonal preparations and is available at a nominal price. In the future, it may be used in several other indications more frequently.

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