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Original Research Article

A study of efficacy of ormeloxifene in abnormal uterine bleeding of ovulatory disorders

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ABSTRACT

Background: Abnormal uterine bleeding (AUB) of ovulatory disorders is defined as the state of abnormal bleeding from the genital tract without any clinically detectable organic, systemic and iatrogenic cause. AUB is one of the common gynaecological issues among the patients visiting the hospital as it could affect at least 1/3rd of women in the child bearing age. Ormeloxifene, a nonsteroidal, nonhormonal and selective estrogen receptor modulator is a highly safe drug in treating acute and abnormal menstrual bleeding.
Methods: The 40 cases of heavy menstrual bleeding (HMB) with ovulatory disorder in the range of 40-52 years of age were treated with 60 mg ormeloxifene twice a week for first 12 weeks and once a week for next 12 weeks. The patients were evaluated for haemoglobin, pictorial blood loss assessment chart (PBAC) score and endometrial thickness before and after treatment.
Results: A significant decrease in endometrial thickness and PBAC score was observed. Also, the level of haemoglobin is found to increase significantly from 8.4±0.8 to 9.9±0.7. In this study, following 6 months of treatment with ormeloxifene, 90% of cases had marked improvement in their symptoms, while 10% of the patients required surgical management i.e., hysterectomy. Amenorrhea was observed in 7.5% of total cases and hypomenorrhea in 5% cases.
Conclusions: Based on these results we could conclude that ormeloxifene could be the drug of choice in patients with AUB as it is very safe with manageable side effects. This simple drug-based therapy has facilitated compliance, tolerability and noticeable reduction of symptoms resulting in satisfaction towards the treatment.

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

INTRODUCTION

Abnormal uterine bleeding (AUB) of ovulatory disorder is defined as the state of abnormal bleeding from genital tract without any clinically detectable organic, systemic and iatrogenic cause.[1] It is one of the most common gynaecological problems for which patients visit the hospital. It affects almost 1/3rd of the women of child bearing age group.[2]

Ovulation disorders like oligovulation, anovulation, polycystic ovarian changes and corpus luteal dysfunction may result in AUB which is known as AUB of ovulatory disorders.[3] The patient presents with prolonged and HMB; which is more than 8 days in duration or more than 80 ml of blood loss or both which leads to anaemia.[4] Alteration in hypothalamic-pituitary-ovarian function or change in prostaglandin levels are the main cause for AUB. It causes heavy profuse bleeding.

AUB is more common in anovulatory cycles than in ovulatory cycles. Though various medical managements have been devised to treat the condition, hysterectomy remains as a last resort in women who do not desire fertility. But this being a surgical procedure, has its own share of complications like premature menopause, bladder and bowel complications.[5]

An emerging drug therapy with ormeloxifene, a SERM, though having limited studies, has proven to be effective. Ormeloxifene is a non-steroidal, non-hormonal, 3rd generation SERM with estrogen like effect in vagina, bone, central nervous system, cardiovascular system anti-estrogenic effect in breast and uterus.[6] It has an added benefit of minimising dysmenorrhoea and premenstrual syndrome by its action on the endometrial estrogen receptor (ER).[7]

It is licensed under Novex-DS, Centchroman and Sevista. Side effects include nausea, headache, and delayed menstruation. As stated, the side effects for ormeloxifene are less and easily manageable. According to resources available, ormeloxifene have longest safety margin, the cost of the drug is comparatively less than hysterectomy and have lesser side effects than hysterectomy which is a surgical procedure.[5] With this in view this study was conducted to assess the efficacy of ormeloxifene in management of cases with HMB.

METHODS

A hospital-based cohort study was conducted in an outpatient and inpatient department of obstetrics and gynaecology, Sri Venkateshwaraa medical college, hospital and research centre, Puducherry among perimenopausal women who presents in OPD with HMB fulfilling the inclusion and exclusion criteria for a period of 18 months in 40 cases with HMB.

Inclusion criteria

Perimenopausal women aged between 40 to 52 years with HMB (cyclical/non-cyclical) were included in the study.

Exclusion criteria

Cases with uterine size >12 weeks, adnexal mass, breast malignancy or genital malignancy, pregnancy, patients with liver disorders/ cardiac disorders/ metabolic disorders/ renal disorders/ coagulative disorders, patients who are allergic to ormeloxifene were excluded from the study.

Data collection

Patients attended both outpatient and inpatient department of obstetrics and gynaecology with HMB during the months of November 2019 to May 2021 were included in the study. The individual participants were explained about the study and they were also assured that, their identity would be kept strictly confidential and they had given the option to refuse participation in the study. Written and informed consent was obtained from the study participants prior to the interview. Both the English and Tamil formats of the Informed consent are enclosed.

Perimenopausal women with complaints of HMB who have given the written informed consent were selected for the study. On admission, details like age, obstetric, medical and menstrual history were documented. General examination, per abdomen and bimanual examinations were performed.

The menstrual blood loss was assessed by PBAC. All routine investigations like haemoglobin and PCV (to know the severity of anemia), blood grouping and typing were done. Endometrial sampling (to know the basic endometrial pattern), transvaginal ultrasound (to rule out other pelvic pathologies) and other relevant investigations were documented.

All 40 cases of HMB with ovulatory disorder between the ages of 40-52 years who completed child bearing were treated with ormeloxifene 60 mg orally twice a week for 12 weeks, followed by once a week for another 12 weeks.

Patients were reviewed at the end of 1st, 4th and 6th month of the study. Then after 6 months, haemoglobin, PCV, transvaginal ultrasound and endometrial sampling were repeated.

Their endometrial thickness and haemoglobin levels were determined at the start of the study and also at 6 months and the both were compared and assessed.

Statistical analysis

All data are entered in a Microsoft excel sheet and statistical analysis was made by SPSS version 23. Descriptive statistics and paired T test were used to analyze the data. If, p value is less than 0.05, then it is considered significant.

RESULTS

In this study to know the efficacy of ormeloxifene in AUB of ovulatory disorders among perimenopausal women there were 65% of the patients in the age range of 40 to 45 years and 35% of the patients were between 46 to 50 years of age group. The mean age among the study participants was found to be 44.2±2.7 years. Regarding the parity 50% of the women had two children while 45% of the study women had three children. Parity status was four and five among 2.5% of the women each.

Based on the days of menstrual cycle for 55% of the peri menopausal women the flow was less than or equal to 10 days and for 45% 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 12.3±3.7 days/ cycle. Menstrual cycle length was less than 35 days for 87.5% of the cases and more than 35 days for 12.5% of the cases in this present study.

The mean menstrual cycle length was 32.2±4.7 days among the perimenopausal women. In this present study duration of complaints was 1-6 months for 60% of the

cases, 7-12 months for 35% of the cases and more than 12 months for 5% of the cases. The mean duration of complaints among the study population was noted to be 7.6±4.7 months.

In this current study, following treatment with ormeloxifene, amenorrhea was present among 7.5% of the cases and 92.5% of the cases had no amenorrhea. Hypomenorrhoea was noted among 5% of the women in this study while 95% of the women had no hypomenorrhoea. Around 5% of the participants had nausea whereas 95% of the participants had no sense of nausea or vomiting. Headache was present among 2.5% of the patients.

Among the study participants 42.5% of them had proliferative endometrium, 22.5% of the patients were diagnosed to have disordered proliferative endometrium and another 22.5% of the patients had Simple endometrial hyperplasia. Disordered endometrium was seen in 12.5% of the cases.

Table 1: Endometrial findings among the study participants.

ET0	Frequency	Percent (%)
Disordered endometrium	5	12.5
Disordered proliferative endometrium	9	22.5
Proliferative endometrium	17	42.5
Simple endometrial hyperplasia	9	22.5
Total	40	100

In this study following 6 months of treatment with ormeloxifene, 90% of cases had marked improvement in their symptoms whereas 7.5% of cases had mild improvement and 2.5% of cases had no improvement in their symptoms.

Table 2: Proportion of cases with Improvement in symptoms.

Improvement	Frequency	Percent (%)
No improvement	01	2.5
Mild improvement	03	7.5
Marked improvement	36	90
Total	40	100

On assessing the Hb level at the time of initiation of the study the mean Hb was found to be 8.4±0.8 gm% while the Hb levels after 6 months of treatment with ormeloxifene was seen to be 9.9±0.7 gm%. The difference in mean Hb level before and after treatment was statistically significant with p=0.000, which shows Hb levels had improved better after treatment with ormeloxifene.

Table 3: Difference in Hb level before and after treatment with ormeloxifene.

Hb at start of study	Hb at 6 months	P value
8.4±0.8	9.9±0.7	0.000*

*Significant

The mean transvaginal ultrasound finding of endometrial thickness at the initiation of study was 10.9±0.7 mm and after 6 months of treatment endometrial thickness was found to be 9.0±0.8 mm. there was significant statistical difference noted in TVS finding at the start of study and at 6 months of treatment with ormeloxifene (p=0.008).

Table 4: Difference in ET before and after treatment with ormeloxifene.

ET at start of study	ET at 6 months	P value
10.9±0.7	9.0±0.8	0.008*

*Significant

Mean PBAC finding for menstrual blood loss at the start of study was 206.9±14.2 and at 6 months of treatment was noted as 81.1±29.1. there was significant difference in blood loss noted before and after treatment with ormeloxifene, blood loss has been reduced drastically with treatment (p=0.000).

Table 5: Difference in PBAC finding before and after treatment with ormeloxifene.

PBAC at start of study	PBAC at 6 months	P value
206.9±14.2	81.1±29.1	0.000*

*Significant

In the present study, 90% of cases were successfully treated with ormeloxifene-medical management however, 10% of cases required abdominal hysterectomy-surgical management in a result of managing DUB.

Table 6: Need for surgical management.

Treatment modality	Frequency	Percent (%)
Conservative management	36	90
Surgical management (Abdominal hysterectomy)	04	10
Total	40	100

DISCUSSION

AUB-O is more prevalent in the first five years after a woman begins menstruating and as she approaches menopause, although it can happen at any time throughout this period. Pharmacological therapies are presently the sole alternatives for women with AUB-O who want to keep their fertility. Some of the other pharmacological treatments are exclusively effective for anovulatory AUB,

whereas others may be beneficial for both. Pharmacological therapies such as NSAIDS, oral contraceptive tablets, progestins, danazol, GnRH agonists, and antifibrinolytic medicines all help to lower menstrual blood loss, but their benefits are only temporary.

In this study to know the efficacy of ormeloxifene in AUB of ovulatory disorders among perimenopausal women there were 65% of the patients in the age range of 40 to 45 years and 35% of the patients were between 46 to 50 years of age group. The mean age among the study participants was found to be 44.2±2.7 years.

Among the study participants 42.5% of them had proliferative endometrium, 22.5% of the patients were diagnosed to have disordered proliferative endometrium and another 22.5% of the patients had simple endometrial hyperplasia. Disordered endometrium was seen in 12.5% of the cases. In this study following 6 months of treatment with ormeloxifene, 90% of cases had marked improvement in their symptoms whereas 7.5% of cases had mild improvement and 2.5% of cases had no improvement in their symptoms.

In this current study amenorrhea was present among 7.5% of the cases. Hypomenorrhoea was noted among 5% of the women in this study and 5% of the participants had nausea while only 2.5% of the patients gave history of headache with treatment.

On assessing the Hb level at the time of initiation of the study the mean Hb was found to be 8.4±0.8 gm% while the Hb levels after 6 months of treatment with ormeloxifene was seen to be 9.9±0.7 gm%. The difference in mean Hb level before and after treatment was statistically significant, which shows Hb levels had improved better after treatment with ormeloxifene.

The mean transvaginal ultrasound finding of endometrial thickness at the initiation of study was 10.9±0.7 mm and after 6 months of treatment endometrial thickness was found to be 9.0±0.8 mm and there was significant statistical difference noted in TVS finding at the start of study and at 6 months of treatment with ormeloxifene.

Mean PBAC finding for menstrual blood loss at the start of study was 206.9±14.2 and at 6 months of treatment was noted as 81.1±29.1. There was significant difference in blood loss noted before and after treatment with ormeloxifene, blood loss has been reduced drastically with treatment.

We investigated the efficacy of ormeloxifene in AUB-O patients, and our findings indicated that there was a considerable reduction in menstrual blood loss, which is consistent with prior research.[17,18]

Also, the findings of the present study were comparable with the findings of the following studies. Agarwal et al reported that at 3 months, ormeloxifene reduced the mean PBAC score substantially more than norethisterone.[8] Ormeloxifene caused a greater increase in Hb concentration and a smaller decrease in ET than norethisterone. Ormeloxifene provided substantially higher improvement after 6 months, in their study. Also, they stated that there were no adverse events reported in both the groups. They came to the conclusion that while both medicines are successful in treating DUB, ormeloxifene outperforms norethisterone in terms of lowering menstrual blood loss.

In another study, Dhananjay et al reported that after therapy with ormeloxifene, there was a considerable improvement in Hb g/dl and a significant decrease in ET compared to tranexamic acid, in their study.[3] Komaram R et al[5] reported that with the use of ormeloxifene in DUB, the median PABC score decreased significantly from baseline to the 25th week of therapy follow-up, and the decline was statistically significant. When compared to the mean baseline value, the mean ET decreased significantly after treatment with ormeloxifene, in their study. The change in mean Hb levels between baseline and post-treatment was determined to be statistically significant at 1.3 gm/dl. A considerable improvement was seen, with 84% patients experiencing relief from dysmenorrhoea. The individuals in this trial had no serious adverse effects.

Also, Singh et al stated that with the treatment of ormeloxifene the difference in median PBAC score between pretreatment and post-treatment was determined to be significant.[2] Similarly, the difference in mean Hb between pre- and post-treatment levels was the same, in their study. In comparison to pre-treatment, the frequency distribution of clots was significantly different after therapy.

Masand et al stated that PBAC score was significantly reduced in ormeloxifene-treated individuals.[9] In women using ormeloxifene, there was a statistically significant increase in Hb and a drop in ET, in their study. In addition, 6.5 percent of cases did not respond, and 8.7 percent were lost to follow-up. Also, 2.2% cases underwent hysterectomy during the one-year study period, in their study. Amenorrhea was the most commonly reported adverse effect.

Anjum et al reported that the difference between the pre-treatment and post-treatment median PBAC scores was substantial.[10] They claimed that after four months of therapy, 81.3% women in their trial were free of menorrhagia, in their study. In two cases, there was no reaction and hysterectomy was performed. Vaginal discharge, unexplained stomach discomfort, gastrointestinal distress, headache, and ovarian cysts were among the side effects.

Also, Suhasini et al reported that at the end of 6 months, the mean PBAC scores in each group revealed a reduction in blood loss of 86.64% ormeloxifene 60 mg group and 87.69% ormeloxifene 30 mg group.[11] Both groups had

similar reductions. When comparing the reductions in the ormeloxifene 60 mg and ormeloxifene 30 mg groups, the difference was significant, in their study. As a result, ormeloxifene 30 mg group B might be suggested for the treatment of DUB.

Kumari et al reported that in DUB with the use of ormeloxifene, after six months, the median PBAC score dropped from 265 to 27.[12] At 6 months, the mean hb concentration had grown considerably from 9.15 g/dl to 10.36 g/dl, in their study. After 6 months, the mean ET has decreased from 11.81 mm to 7.63 mm, in their study. Also, 84% women reported a significant improvement in their symptoms. The medication has no significant negative effects, in their study.

Hymavathi et al reported that at six months, the drop in the mean PBAC score with ormeloxifene was substantially greater than that with tranexamic acid, in their study.[13] Ormeloxifene caused a greater increase in Hb concentration and a lower drop in ET than tranexamic acid, in their study. Ormeloxifene provided significant relief from dysmenorrhoea as well as subjective improvement.

Also, Agrawal et al reported that after 6 months of treatment, the drop in mean PBAC score with ormeloxifene was substantially greater than that found with norethisterone.[14] When compared to norethisterone, ormeloxifene resulted in a substantial rise in Hb levels and a decrease in ET, in their study. Because of the greater tolerance and flexible dose schedule, patients were more cooperative with ormeloxifene. They came to the conclusion that ormeloxifene was more successful than norethisterone in lowering blood loss, improving Hb levels, and reducing ET in DUB cases, in their study.

Arunadevi et al noted consistent reduction in the thickness of the endometrium and notable level of improvement in Hb in ormeloxifene treated cases compared to cases treated with OCPs, in their study.[15] They concluded that ormeloxifene is efficacious than oral contraceptive pills in the management of DUB.

Varwatte et al noted that the average age of the research participants was 36 years.[16] Between pre-treatment and 3 months and 6 months after treatment, there was a significant difference in mean Hb, mean ET, and mean PABC score. As the length of therapy was prolonged from 3 months to 6 months, mean Hb concentration increased while mean ET and mean PABC score dropped, in their study.

CONCLUSION

The drug of interest ormeloxifene, is a non-steroidal and non-hormonal drug which is safe both metabolically and pharmacologically and can also protect breast and endometrium. The administration of ormeloxifene, has greatly reduced the blood loss in patients with AUB, which is demonstrated with the decrease in PBAC score, decreased endometrial thickness, reduction in blood clots and with substantial increase in haemoglobin levels. By using ormeloxifene, the desirable side effects like amenorrhea or hypomenorrhea were observed in women of the perimenopausal age group and in women who couldn't undergo surgery. Additionally, there was a significant drop in hysterectomy percentage in patients who were treated with ormiloxifene, resulting in decreased morbidities associated with the surgery. The simple drug administration method has facilitated the compliance, tolerability and noticeable reduction of symptoms resulting in satisfaction towards the treatment. The patient compliance is very good as could observe the improvement without the need for any additional surgery. Ormeloxifene should be the drug of choice in patients with AUB as it is very safe with manageable side effects. It can be administered in patients who have crossed their child bearing age but should be used cautiously with proper counselling in the perimenopausal age group.

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