International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Chandran RS et al. Int J Reprod Contracept Obstet Gynecol. 2024 Aug;13(8):2065-2069
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20242072

Original Research Article

Ormeloxifene in the management of abnormal uterine bleeding in tertiary care centre South Kerala

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Received: 15 May 2024
Revised: 20 June 2024
Accepted: 28 June 2024

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ABSTRACT

Background: AUB is the most common presentation in the reproductive age group. Many females suffer from AUB and its related effects. A study on the effectiveness of an easily available drug (ormeloxifene) with an easy dosing schedule was done and its wonderful role in controlling the symptoms and improvement of quality of life of a female with no financial burdens and surgical morbidity was studied.
Methods: A hospital based prospective observational study was conducted among women attending the outpatient clinic of OBG department at Dr Somervell Memorial CSI Medical College, Karakonam, Trivandrum district.
Results: Total 50 women with AUB took part in the study. 62% had menstrual duration of <7 days with regular cycles (84%). 86% of them had history of passage of clots. 48% of them had dysmenorrhea. Efficacy of ormeloxifene was assessed by using PBAC score and haemoglobin level measurement. A repeated measures ANOVA with a Greenhouse-Geisser correction determined mean PBAC score differed significantly between months. Post hoc analysis with a Bonferroni adjustment revealed PBAC score was statistically significantly decreased from pre-intervention to 3 months to 6 months. There is statistically significant difference with respect to haemoglobin level improvement.
Conclusions: Ormeloxifene is an excellent drug in controlling AUB as evidenced by the PBAC score and haemoglobin levels. Ormeloxifene has better compliance and acceptability. It is cost effective with a simple dosage schedule. A significant decrease in the menstrual blood loss and marked improvement in the hemoglobin concentration.

Keywords: Abnormal uterine bleeding, Haemoglobin, Ormeloxifene, Reproductive age goup

INTRODUCTION

Abnormal uterine bleeding is the most common presentation in the reproductive age group. It describes a spectrum of abnormal bleeding patterns that occur in anovulatory women with no significant medical comorbidities or pelvic pathology. Mechanism in anovulatory bleeding differ, but each reflects an unusual pattern of steroid hormone stimulation that deviates from the sequence involved in the normal menstrual cycle. Anovulatory bleeding can be effectively and confidently managed with medical regimen based on sound physiologic concepts. First is to reverse the abnormalities of endometrial growth and development that results from chronic anovulation and predispose to excessive and prolonged menstrual flow.[1] A reliable drug for management of abnormal uterine bleeding should meet the requirements like the drug should be effective, convenient to take, cost should be low, have minimal side effects and should have long safety margin.[2] Ormeloxifene (also known as Centchroman) is one of the selective estrogen receptor modulator (SERM) a class of medications which acts on the estrogen receptor (ER).[3] It is a non-steroidal, non-hormonal oral contraceptive developed by Central Drug Research Institute, Lucknow.[4] Very few studies are available on ormeloxifene for the treatment of abnormal

uterine bleeding. In this era of organ conservation ormeloxifene can serve as a good alternative to operative management. With this background, the present study was done in south kerala population to evaluate the proportion of patients getting better with ormeloxifene in the management of abnormal uterine bleeding.

METHODS

A hospital based prospective observational study was conducted among women attending the outpatient clinic of Obstetrics and Gynaecology department in Dr Somervell Memorial CSI medical college, Karakonam, Trivandrum district from August 2018 to November 2021 after getting approval from Institutional Ethics Committee (IEC No: SMCSIMCH/EC(PHARM)03/09/28**).**

All women above the age of 35 years and who fulfils the operational definition of abnormal uterine bleeding [the average cycle length is about 28 days with a range from (21-35) days. The number of bleeding days may vary from 2-6. The upper limit of blood loss in a normal menstruation is considered as 80ml. Any bleeding outside the above specified normal limits is termed abnormal uterine bleeding] and those who have completed family and those women with no underlying co-morbidities were included in the study. Women with diagnosed cases of uterine fibroid (≥12wks size), uterine polyp, liver diseases, renal diseases, adnexal masses, breast malignancy and genital malignancy, pregnant, lactating women in first 6 months, IUCD users, OCP users, and also patients with severe bleeding and wanting emergency treatment, and those with Haemoglobin <5gm% were excluded from the study.

Based on a previous study done, considering the proportion of improvement in abnormal uterine bleeding following administration of ormeloxifene as 95.8% in a study done in a tertiary care centre in Andhra Pradesh, allowable error of 6% of proportion, the sample size calculated to be 50.[1] Every consecutive patient who comes to the outpatient clinic and fulfils the inclusion criteria was included in the study. The written informed consent was taken from all the study participants. Detailed gynaecological examination and investigations was done to rule out any uterine pathology, congenital malformation and other organic causes for AUB.

Patient enrolled for the study was given 60mg tablet of ormeloxifene-two times a week for initial 3 months following which dose reduced to once per week for next 3 months. Patient had been called at an interval of 1 month, 3 months and 6 months to assess their menstrual blood loss and duration of cycles, details was recorded in the case sheet, which the principle investigator reviewed to determine the effect of drug. All participants are advised to use napkins having similar absorbent capacity. In case of development of any untoward side-effect or any excessive bleeding they were asked to review in gynaecology casualty. Contact number of all participant are collected in the initial visit itself and we make sure that they all take drugs correctly. Endometrial sampling was done and hyperplasia and malignancy was ruled out before commencement of ormeloxifene treatment.

Data collection was done by one-to-one interview method using a predesigned, semi-structured questionnaire. Privacy and confidentiality of the study subjects were maintained. Women were subjected to detailed history including age, parity and height. Family history, menstrual history, past obstetric history, past medical history, was taken. Systemic examination with special reference to pallor, pulse rate, blood pressure and abdominal examination was carried out and routine blood investigations were done. Amount of blood loss during the periods were calculated using pictorial blood loss assessment chart (PBAC) complete blood count, coagulation profile, thyroid profile, blood sugar, liver function test, renal function test, ultra-sonogram of the pelvis and transvaginal ultrasound measurement of endometrial thickness was done.[5]

The pre-treatment and post treatment menstrual blood loss and haemoglobin level were compared. Any unpleasant feelings following the drug intake was also asked for. If no cessation in bleeding within 7 days following intake of ormeloxifene-additionally tranexemic acid was given and those patients were excluded from the study sample. Any patient who did not turn up for review was contacted.

The collected data was entered into MS Excel Sheet 2019, and analysed using SPSS version 22. All qualitative and quantitative variables were expressed as frequency and percentages and mean and standard deviation respectively. Repeated measures ANOVA and paired t test was used to find the effectiveness of ormeloxifene on menstrual blood loss. For all statistical interpretations, $p<0.05$ was considered the threshold for statistical significance.

RESULTS

Total 50 women with abnormal uterine bleeding were participated in the study and their mean age was found to be 43.08±3.91 years. Majority (64%) of the study subjects studied up to high school and more than three forth (80%) of them were housewives (Table 1).

Majority of the study subjects reported that they had menstrual duration of <7 days (62%) and had regular menstrual cycles (84%). More than quarter (32%) of the study subjects used >5 pads per day. More than three forth (86%) of the study subjects had history of passage of clots during periods. Near to half (48%) of the study participants had dysmenorrhea and among them about 16.7% had congestive type of dysmenorrhea (Table 2).

Efficacy of ormeloxifene in the management of abnormal uterine bleeding among the study subjects was assessed by using PBAC score and haemoglobin level measurement. A repeated measures ANOVA with a Greenhouse-Geisser correction determined that mean PBAC score differed

significantly between months following intake of Ormeloxifene (F (1.19,58.69) = 134.85, p <0.05). Post hoc analysis with a Bonferroni adjustment revealed that PBAC score was statistically significantly decreased from pre-intervention to 3 months (312 (95% CI, 244.77 to 379.23), p <0.001, from pre-intervention to 6 months (346.48 (95% CI, 276.97 to 415.99), p<0.001 and from 3 months to 6 months (34.48 (95% CI, 9.81 to 59.15), p 0.003) (Table 3 and Table 4).

Table 1: Distribution of study subjects based on demographic characteristics (n=50).

Variables	Frequency	Percentage (%)
Age (years)		
30-35	1	2
36-40	11	22
41-45	23	46
46-50	15	30.
Education		
Primary	2	4
High school	32	64
Diploma	12	24
Graduate	4	8
Occupation		
Clerical	5	10
Business	4	8
House wife	40	80
Others	1	2

Table 2: Distribution of study subjects based on menstrual history details.

Variables	Frequency	Percentage (%)
Menstrual duration (days)		
<7	31	62
7-9	16	32
>9	3	6
Regularity of menstrual cycles		
Regular	42	84
Irregular	8	16
Number of pads used per day		
2-3	7	14
4-5	27	54
>5	16	32
Clot passage		
Present	43	86
Absent	7	14
Dysmenorrhea		
Present	24	48
Absent	26	52
Type of dysmenorrhea (n=24)		
Spasmodic	20	83.3
Congestive	4	16.7

Table 3: Efficacy of ormeloxifene in the management of abnormal uterine bleeding among the study subjects using PBAC score (n=50).

PBAC score	Mean	Standard deviation	F	P value
Baseline	402.20	202.71	134.85	<0.001*
3 months	90.20	53.13		
6 months	55.72	71.71		

*p value <0.05 was statistically significant; Test used: repeated measures ANOVA

Table 4: Post hoc test for the efficacy of ormeloxifene in the management of abnormal uterine bleeding among the study subjects using PBAC score.

PBAC score comparisons	Mean difference	SE	P value
Baseline and 3 months	312.00	27.12	<0.001
Baseline and 6 months	346.48	28.04	<0.001
3 months and 6 months	34.48	9.95	0.003

Table 5: Efficacy of ormeloxifene in the management of abnormal uterine bleeding among the study subjects using haemoglobin level.

Haemoglobin (g/dl)	Mean	Standard deviation	t value	P value
Baseline	9.11	1.78	9.45	<0.001
6 months	11.53	1.27		

DISCUSSION

Abnormal uterine bleeding can happen at any time, although it usually happens five years after a woman begins her menstrual cycle and as she gets closer to menopause. Pharmacological methods are presently the only ones accessible for women with DUB who want to maintain their fertility. Some pharmacological medications are good only for ovulatory DUB, some are effective only for anovulatory dysfunctional uterine bleeding, and some may be useful for both. Menstrual blood loss can be decreased by pharmacological drugs like NSAIDS, oral contraceptives, progestins, danazol, GnRH agonists, and antifibrinolytic medications; however, their benefits are only temporary. Our analysis of the efficacy of ormeloxifene in treating patients with dysfunctional uterine bleeding revealed a noteworthy decrease in monthly blood loss.

In the current study, there was a significant reduction in PBAC score from baseline to 3rd month and 6th month of ormeloxifene treatment follow-up (from 402.20±202.71 to 55.72±71.71) and this reduction was found to be statistically significant (p value <0.001). Similar finding was observed in a study done among patients with dysfunctional uterine bleeding attending the out-patient department of Obstetrics & Gynaecology at King George Hospital, Visakhapatnam, Andhra Pradesh, where the

median PBAC score was statistically significantly reduced from baseline following treatment (p<0.001). The median PBAC score was reduced from 265 to 27 (p<0.001), showing a reduction of 89.81% after 24 weeks according to a study conducted by Archana Kumari and Ritika Prakash in Rajendra Institute of Medical Sciences, Ranchi.[2] Biswas et al found that the median PBAC score was reduced from 272 to 107.8 at the end of 6 months of treatment, showing a reduction of only 60.37% in the menstrual blood flow.[3] Kriplani et al did a pilot study in which the median PBAC score was statistically significantly reduced from 388 to 5 at 16 weeks with 98.7% reduction (p<0.001).[4] Bhattacharyya et al in his study, where 180 dysfunctional uterine bleeding cases in 3 groups were administered ormeloxifene, norethisterone and iron, concluded a marked decrease in mean PBAC score from 108.70 to 62.48 in the ormeloxifene group, but in norethisterone group, it was decreased only to 94.07 from 113.87.[5] Shravage et al found an 85.7% reduction in menstrual blood loss (mean PBAC score from 262 to 73) after 3 months of therapy as compared to 54.67% with medroxyprogesterone.[6] In another comparative study by Agarwal et al, there was 61.1% decrease in menstrual blood loss (mean PBAC score from 216 to 84) in ormeloxifene group compared to 26.7% with norethisterone (mean PBAC score from 232 to 170).[7] Thus, from all these studies, ormeloxifene significantly reduces menstrual blood loss in dysfunctional uterine bleeding.

In our study the mean haemoglobin level at the end of 24 weeks after treatment with ormeloxifene was 11.53±1.27g/dl compared to the pre-treatment level of 9.11±1.78g/dl. The increase in haemoglobin was 2.42 g/dl at the end of 24 weeks (p<0.001). According to a study conducted by Archana Kumari and Ritika Prakash in Rajendra Institute of Medical Sciences, Ranchi, the mean haemoglobin level at the end of 6 months after treatment with ormeloxifene was 10.36 g/dl compared to the pre-treatment level of 9.15 g/dl. The increase in haemoglobin was 1.21 g/dl at the end of 6 months (p<0.001).[1] In a hospital-based cohort study conducted by Nandhini GM and her collegues among perimenopausal women with heavy menstrual bleeding in a tertiary care centre in Puducherry, where their mean Hb level at the time of initiation of the study was found to be 8.4±0.8 gm/dl while the Hb levels after 6 months of treatment with ormeloxifene was seen to be 9.9±0.7 gm/dl. The difference in mean Hb level before and after treatment was found to be statistically significant, which shows Hb levels had improved better after treatment with Ormeloxifene.[9] In a study conducted by Dhananjay and colleagues, there was a statistically significant increase in Hb concentration (8.26 to 10.59 g/dL; p<0.001).[10] Similar increase in Hb level was found in other studies too.

Our research was limited by the absence of follow-up after the 6-month study period, which made it impossible to comment on whether or not menstrual cyclicity returned to normal. Long-term follow-up is necessary to monitor the drug's effectiveness and to record any recurrence of symptomatology. The study group consisted of 50 women who met the inclusion criteria, and they were a small study group in south Kerala. Regular hysteroscopic evaluation was not performed, and endometrial thickness was not a parameter of the study to compare the pre- and post-treatment outcomes.

The PBAC score and higher haemoglobin levels support the conclusion that Ormeloxifene, a non-steroidal, non-hormonal agent is an excellent medication for controlling abnormal uterine bleeding without affecting normal endocrine and physiological parameters.

CONCLUSION

Ormeloxifene is an excellent drug in controlling Abnormal uterine bleeding as evidenced by decrease in the PBAC score and improvement in haemoglobin levels. Ormeloxifene has better compliance and acceptability. It is cost effective with a simple dosage schedule. A significant decrease in the menstrual blood loss and marked improvement in the hemoglobin concentration was noted from the pretreatment period to 3rd month and 6th month follow up. Majority of the study population had symptomatic relief and quality of life improved in a span of 6 months.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Chandran RS, Adaline Thangam TF, Joy DP, Rose A. Ormeloxifene in the management of abnormal uterine bleeding in tertiary care centre South Kerala. Int J Reprod Contracept Obstet Gynecol 2024;13:2065-9.