

Study of Efficacy and Safety of Ormeloxifene in Management of Abnormal Uterine Bleeding

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ABSTRACT

Introduction: Abnormal uterine bleeding (AUB) is one of the most common conditions for which women consult their gynaecologists. Study was done to evaluate the efficacy and adverse reactions of ormeloxifene in patients with abnormal uterine bleeding.

Material and Methods: This was single centred, open label, 6 months prospective study. 53 patients with complaints of abnormal uterine bleeding having PBAC Score more than 100 were enrolled in study. Ormeloxifene 60mg twice a week was given for 3 months followed by 60 mg once a week for next 3 months. At follow ups, patients were assessed for Endometrial thickness by USG, Haemoglobin level, PBAC score and adverse effects of drug therapy.

Results: A total 53 patients with the mean age of 32.91±6.82 were enrolled, in which 45 patients completed the follow up. There was statistically significant decrease in endometrial thickness, haemoglobin level and PBAC score.

Conclusion: Thus Ormeloxifene, a non-steroidal, non-hormonal agent, with its convenient dose schedule provides effective and favourable medical treatment.

Keywords: Abnormal Uterine Bleeding, PBAC Score, Ormeloxifene

INTRODUCTION

Abnormal uterine bleeding (AUB) may be defined as any variation from the normal menstrual cycle, including alteration in regularity, frequency of menses, duration of flow and amount of blood loss.¹ Basically it is a symptom and not a disease. It can be of two types anovulatory and ovulatory. Anovulatory AUB, commonly seen at both ends of the reproductive years because of hypothalamic immaturity and changes associated with menopause, is usually treated effectively by replacing the missing component, progesterone, in the luteal phase. The mechanism for ovulatory AUB is less well understood. AUB can occur at any age in various forms and has different modes of presentation.^{2,3} Abnormal uterine bleeding during reproductive age can result from a broad spectrum of conditions ranging from physiological process to malignant lesions involving organic, systemic, and hormonal responses. It may be due to fibromyoma, adenomyosis, endometrial polyp, ovarian tumor, pelvic inflammatory disease (PID), endometrial hyperplasia, endometrial carcinoma, hormonal imbalance (like hypothyroidism), or hypothalamo pituitary ovarian axis disturbances.^{4,5,6}

About 9 to 16% of women experience episodes of abnormal uterine bleeding at sometimes during the reproductive years of life. It is common during extremes of reproductive life, following pregnancy and lactation.⁷ It is generally agreed

that a normal bleeding episode comprises a menstrual blood loss volume in the range of 30–40 mL with an upper limit of 80mL.

Approximately 4–8% of women report having menstrual periods longer than 7–8 days when interviewed. A total of 18 epidemiologic studies were identified reporting a world wide prevalence rate of AUB of between 4 to 52%.⁸ Although in the WHO multi country study the three month, self-reported prevalence of excessive bleeding was higher, ranging from 8% to 27%. The frequency increases when the sample is limited to older women.⁹

The traditional treatment for AUB is hysterectomy. But it is suitable only for those who have completed their family. The procedure involves major surgery with significant postoperative morbidity. In recent years, concern has been about possible long term complications of hysterectomy. Thus women are looking forward to an effective medical therapy. The main concern of women regarding this is to retain their fertility. So the techniques like endometrial ablation an alternative to surgical option has reduced postoperative morbidity. This may be unsuitable for women wishing to retain their menstrual or reproductive functions and require technical expertise. So for the women who wish to retain her fertility, conservative treatment is good option. In our study we had seen effects of Ormeloxifene treatment in patients of abnormal uterine bleeding on endometrial thickness, haemoglobin, PBAC Score. In India, Ormeloxifene has been available as a birth control product since the early 1990s. DL-Centchroman (INN:ormeloxifene;trans-7-methoxy-2,2-dimethyl-3-phenyl-4-[4-(2pyrrolidinoethoxy)phenyl] chroman hydrochloride) is a nonsteroidal selective estrogen receptor modulator and once-a-week oral contraceptive agent developed by the Indian Central Drug Research Institute (Lucknow, India).¹⁰⁻²⁰ It is a Selective estrogen receptor modulator is efficiently used for abnormal uterine bleeding. SERM popularly known as Designer estrogens or Fantasy estrogens because they selectively bind with high affinity to estrogen receptors and act as estrogen agonist in some tissues and estrogen antagonist in others so in some

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parts of the body, its action is oestrogenic (e.g., in the bones), In other parts of the body, its action is anti-oestrogenic (e.g., in the uterus and the breasts). It causes an asynchrony in the menstrual cycle between the ovulation and the development of the uterine lining, since it affects ovulation and thins out uterine lining it acts effectively in reducing heavy menstrual bleed, although its exact mode of action has not been well defined. In clinical trials, it caused the ovulation to occur later than it normally would, in some women but did not affect the ovulation in a majority of the women, while causing the lining of the uterus to build more slowly. It speeds the transport of any fertilized egg through the fallopian tubes more quickly, than is normal. Presumably, this combination of effects creates an such an environment that if fertilization occurs, an implantation will not be possible.^{21,22} Study was done to evaluate the efficacy and adverse reactions of ormeloxifene in patients with abnormal uterine bleeding.

MATERIAL AND METHODS

The study was conducted after approval from institutional ethical committee. It was interventional, non blind study of duration of one year from November 2016 to October 2017. Patients diagnosed case of abnormal uterine bleeding attending outpatient department of Obstetrics and Gynaecology Swaroop Rani Nehru hospital, an associated tertiary care centre of Moti Lal Nehru Medical college Allahabad were included in study.

Patients included women aged ≥ 18 to $45 <$ years with a newly diagnosed case of abnormal uterine bleeding, must be able to understand and follow study related advice, informed consent was taken from the patient.

Patient not included in study were not willing to give consent, aub as a result of pregnancy and puerperal complications, bleeding disorders, females having haemoglobin < 6 gm/dl, medical disorders like liver dysfunction, heart disease, migraine, stroke, renal disease, hypo/hyperthyroidism.

Patients were diagnosed as AUB on the basis of history and clinical examination accompanied with routine and specific investigations blood group, Haemoglobin (gm/dl), Rh, TLC, DLC, VDRL, HBsAg, HIV-I and II, fasting and postprandial blood sugar, liver function test, renal function test and complete urine examination. Baseline thyroid function test and urine pregnancy test were done to exclude thyroid disorder and pregnancy. Coagulation profile and bleeding time were done to exclude bleeding disorders. Pap smears were taken and endometrial biopsy was taken.

The drug was administered orally in the form of 60 mg tablet twice weekly (every Monday and Friday) for the first 12 weeks and then once a week (every Monday) for another 12 week.

The patient were asked to use certain sanitary napkins which had similar absorbent capacities and were advised to maintain a menstrual diary to record the total number of days of bleeding, number of sanitary pads used, Number of sanitary pads used each day (24 hour period) were counted. A score for each day was calculated and then score was added up at the end of the month.

Number and sizes of clots passed were also noted and also any episode of flooding. Degree of soaking of each pad, number and size of clots passed.

The follow up visits were conducted at third and six months respectively. Patient were assessed for improvement of symptoms, compliance, regularities. Assessment was done in the form of amount of bleeding (which was assessed by PBAC score), recurrence of symptoms and also the side effects of each drug. Patient's endometrial thickness and haemoglobin were measured after 3 months and 6 months of the treatment.

Menstrual blood loss was measured objectively by pictorial blood loss assessment chart (PBAC) score as described by Higham et al. PBAC is a simple procedure for objective assessment of menstrual blood loss. The subjects were asked to use certain sanitary napkins which had similar absorbent capacities and were advised to maintain a menstrual diary to record the total number of days of bleeding, number of sanitary pads used, degree of soaking of each pad, number and size of clots passed. The Pictorial Blood loss Assessment Chart (PBAC) Scoring was then accordingly to assess menstrual blood loss in each menstrual cycle. A PBAC score > 100 is considered diagnostic for menorrhagia (Higham JM et al 1990).²³

Methods Applied For Various Test

Endometrial Thickness - It was measured in department of radiology Swaroop Rani Nehru Hospital. Endometrial thickness was measured at first visit and then after 3 months and 6 months after treatment ormeloxifene.

Haemoglobin - Sample was given to institutional pathology lab of Swaroop Rani Nehru hospital. Reports were collected from pathology department.

PBAC Score - In this study, objective assessment of menstrual blood loss was done by Pictorial Blood Loss Assessment Chart (PBAC) as devised by Higham et al. PBAC is a simple and less time consuming procedure for objective assessment of menstrual blood loss.

PBAC Score is useful in evaluating menorrhagia in the clinic setting. It can be used as a tool to measure response of menorrhagia to different forms of treatment. Using the scales as described below the total score was calculated by adding up the sum of all scores for the sanitary napkins used in the menstrual cycle.

For sanitary napkins; 1 for lightly stained, 5 for moderately soiled and 20 for completely saturated pads.

Clots are given a score of 1 for small and 5 for large clots.

For flooding a score of 5 is given also.

Possible range of total score is completely dependent on quantitative and qualitative amount of bleeding during menstruation. Abnormal PBAC score ≥ 100 , which correlates with menorrhagia, is defined as ≥ 80 ml of menstrual blood loss.

STATISTICAL ANALYSIS

Microsoft office 2007 was used for the analysis. Chi square test was used for the comparison and calculating p value.

RESULTS

Initially we recruited 53 patients for ormeloxifene in which 45 patients completed study while 8 patients lost in follow up. In those 8 patients, 3 patients had gone through hysterectomy. The present study was conducted on 45 patients. The means age of patients were 32.91 ± 6.82 years and most of the patients (71.11%) from rural area. Most of patients in our study were literate (73.33%). Socioeconomic status of most of patients were lower. Maximum number of the cases in the study were housewives. In our study most of the women presenting with complaint of abnormal uterine bleeding were married, It was further observed in this study that as the parity increased, the abnormal uterine bleeding also increased. Effects of Ormeloxifene treatment on Endometrial thickness, Haemoglobin and PBAC Score were seen in patients of Abnormal uterine bleeding.

The treatment effects of Ormeloxifene in patients of abnormal uterine bleeding, it was found that the endometrial thickness (in mm) has decreased to 7.67 ± 1.30 at 3 months and 6.70 ± 1.21 at 6 months (post-treatment), from the basal value (pretreatment) of 8.97 ± 1.17 (mm). The decrease in endometrial thickness was statistically highly significant in this arm also, on follow up (post treatment) at three months and six months, ($p < 0.001$, significant)

The treatment effects of Ormeloxifene, in patients of abnormal uterine bleeding haemoglobin levels has increased to 8.90 ± 0.83 at 3 months and 9.69 ± 0.90 at 6 months (post-treatment) from the pretreatment (basal value) of 8.11 ± 0.74 (gm/dl). The increase in mean haemoglobin levels was highly significant statistically, on post treatment at three months and six months, ($p < 0.001$, significant).

The treatment effects of Ormeloxifene, in patients of abnormal uterine bleeding it was found that PBAC score

has decreased to 143.09 ± 36.40 at 3 months and 96.33 ± 25.67 at 6 months (post-treatment) from the basal value (pretreatment) of 244.16 ± 37.71 . The decrease in PBAC score was highly significant statistically, at three months and six months (post treatment), ($p < 0.001$, significant). Serious side effects which warrant discontinuation of drug were not seen with ormeloxifene, but few side effects like headache in 1 patient, weight gain in 1 patient, spotting in 2 patients, and amenorrhoea in 5 patients were obtained, also none of the patients in study group developed any significant alteration in liver or renal functions.

DISCUSSION

The normal menstrual cycle consists of 21-35 days, the blood flow lasts 2-7 days and the blood loss is about 20-80 ml in a cycle. The deviation in amount and duration from this normal is recognised as abnormal uterine bleeding. In our study we had seen the treatment effect of Ormeloxifene in patients of abnormal uterine bleeding on Endometrial thickness, Haemoglobin and PBAC Score.

Ormeloxifene is very effective improving all the parameters of blood loss in AUB including the no. of days of bleeding, no. of pads soiled and the passage of clots. Along with being effective, the drug has a good patient acceptability and compliance due to its minimal side effects, low cost (compared to all alternative medical and surgical treatments) and simple dosage schedule.

In our study effect on endometrial thickness of 45 patients was observed, A marked decrease in endometrial thickness in 3 months decrease in endometrial thickness was 14.49% while decrease in endometrial thickness was 25.31% in 6 months, which was comparable with the study of Shazia et al in which decrease in endometrial thickness was 23.64% in 6 months, while in Komaram et al study there was reduction of 20.3%.^{24,25}

Effect of ormeloxifene on haemoglobin in our study that haemoglobin level rised significantly, it was increased 8.87% in 3 months while 16.3% in 6 months, Komaram et al found an increment in haemoglobin from (9.2 to 10.5) gm/ml in 6 months.²⁵ Kriplani et al the mean haemoglobin was increased to 11.2 gm/ml from 10.6 gm/ml in 6 months.²⁶

PBAC score was reduced due to effect of ormeloxifene in our study, decrease in PBAC Score was 41.4% in 3 months while 60.55% in 6 months, while Shravage et al found that reduction in the mean PBAC score was 85.71%, which was more reduction than our study.²⁷

In study of Chhatrala et al decrement in PBAC score was 56.9% in 6 months with ormeloxifene which was comparable to our study.²⁸

CONCLUSION

If we consider costs and complications of surgical treatments, medical therapy should always be tried first in cases of AUB. Medical management has always been the first therapeutic option to be tried and if it fails to show results, one can resort to surgical interventions. Hysterectomy should be the last resort in the management of AUB. The RCOG

Endometrial thickness (mm)	Ormeloxifene effect
Pre treatment (Basal) (mean \pm SD)	8.97 ± 1.17
Post treatment at 3 months (mean \pm SD)	7.67 ± 1.30
Post treatment at 6 months (mean \pm SD)	6.70 ± 1.21
P value	$\leq .0001$

Table-1: Effects of ormeloxifene on endometrial thickness

Haemoglobin	Ormeloxifene effect
Pre treatment (Basal) (mean \pm SD)	$8.11 \pm .74$
Post treatment at 3 months (mean \pm SD)	$8.90 \pm .83$
Post treatment at 6 months (mean \pm SD)	$9.69 \pm .90$
P value	$\leq .0001$

Table-2: Effects of ormeloxifene on haemoglobin

PBAC score	Ormeloxifene treatment
Pre treatment (Basal) (mean \pm SD)	244.16 ± 37.71
Post treatment at 3 months (mean \pm SD)	143.09 ± 36.40
Post treatment at 6 months (mean \pm SD)	96 ± 25.67
P value	$\leq .0001$

Table-3: Effects of ormeloxifene on PBAC score

recommends beginning with medical management before resorting to surgical interventions. While hysterectomy offers an effective cure, it is suitable only for those, who have completed their family and Ormeloxifene has the potential to be an effective treatment for AUB and it should always be considered amongst the all conservative treatment options. Failure to respond to ormeloxifene can be suggestive of some underlying organic pathology and patient needs to be re-evaluated for the same. Though conclusions from the study are limited by small number of subjects, and limited duration of study.

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