ORIGINAL ARTICLE ASIAN JOURNAL OF MEDICAL SCIENCES

Ormeloxifene in acute heavy menstrual bleeding in menopausal transition women

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Submission: 02-05-2021 Revision: 21-07-2021 Publication: 01-08-2021

ABSTRACT

Background: Ormeloxifene, a selective estrogen receptor modulator, is a safer, cost effective and convenient dosing medical therapy in heavy menstrual bleeding of acute abnormal uterine bleeding. **Aims and Objective:** The study aimed to find the effectiveness of Ormeloxifene as 1st line therapy for heavy menstrual bleeding in menopausal transition women to prevent unnecessary hysterectomies and improve quality of life. **Materials and Methods**: This descriptive study was conducted at Lumbini Medical College for a period of one year. Sixty-five cases of acute Abnormal Uterine Bleeding with heavy menstruation during menopausal transition period were provided with Ormeloxifene therapy of 60 milligrams dose two times per week after evaluating pre treatment hemoglobin percentage, Pictorial Blood Loss Assessment Chart (PBAC) score and endometrial thickness. The dose of the drug was reduced to 60 mg weekly after 3rd month if subjective improvement was documented and continued for further 3 months. **Results**: There was a statistically significant reduction in mean PBAC score, mean endometrial thickness and rise in hemoglobin level. Eighty percentages of women had marked subjective improvement of symptoms, 87.7% women had reduction of blood clots, 15. 8% women had relief from dysmenorrheal pain and 50.8% women had regularization of menstrual pattern after 6 months. Amenorrhea (25.3%) was the most common side effect reported in 6 months therapy. **Conclusion**: Ormeloxifene is an effective 1st line medical therapy in acute heavy menstrual bleeding in menopausal transition women.

Key words: Acute abnormal uterine bleeding; Heavy menstrual bleeding menopausal transition; Ormeloxifene; Selective estrogen receptor modulator

Access this article online

Website: http://nepjol.info/index.php/AJMS

DOI: 10.3126/ajms.v12i8.35603

E-ISSN: 2091-0576

P-ISSN: 2467-9100

INTRODUCTION

Heavy menstrual bleeding (HMB) is a common presentation of Abnormal uterine bleeding (AUB); and indication for hysterectomy among late reproductive age group women of Dysfunctional uterine bleeding (DUB).[1-3] Post hysterectomy health hazards to women of menopause transition with sacrifice of ovaries is definitely preventable. First, counseling about the health benefit of utero-ovarian preservation along with financial saving of operative cost; and 2nd, providing better medical treatment option to heavy menstrual bleeding in menopausal transition.[4] Ormeloxifene/Centchroman is a non-steroidal anti-estrogen with almost no side effects due to progesteronal, androgenic and anti-androgenic devoid activities.[5] It is a selective estrogen receptor modulator (SERM), mediates its effects by high affinity interaction with estrogen receptors, antagonizing the stimulating effect of estrogen on uterine tissue. It has neutral effect on vagina, bone, cardiovascular and central nervous system. It is therefore a substitute for treatment of heavy AUB to improve quality of life.[6,7] Treatment of menopausal transition women with Ormeloxifene for acute HMB is a pioneer study in the western Nepal.

The aim of our study is to find out the effectiveness of Ormeloxifene in heavy menstrual bleeding of menopausal transition women as 1st line medical therapy.

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MATERIALS AND METHODS

This descriptive study was conducted at Lumbini Medical College and Teaching Hospital, Palpa, a tertiary hospital of Nepal for a period of one year (September 2018 to August 2019) after the ethical approval. Sixty-five cases of acute AUB with heavy menstrual bleeding (HMB) during menopausal transition period were enrolled from gynecological outpatient department (OPD) after inclusion and exclusion criteria were fulfilled.

Inclusion criteria

Women of age 45±10 years with acute AUB with heavy menstrual bleeding, were selected.

Exclusion criteria

a. Known case of bleeding disorder, recent h/o liver disease, jaundice, obesity, Polycystic Ovarian diseases, migraine, Stroke, platelets disorders, Coagulopathy, Previous history of thrombosis and medications resulting bleeding/coagulation disorder.
b. Cervicitis/cervical dysplasia and Pelvic pathologies i.e. uterine fibroids, adenomyosis, malignancies of uterus/cervix/ovary/vagina/endometrial hyperplasia with atypia.
c. Thyroid diseases, heart diseases and renal disease.
d. Pregnancy, its related complications and lactating mother
e. Use of contraceptive methods: IUCDs or oral contraceptives.

Analysis

Sample size was calculated from the Fisher's formula, n=Z2P (1-P)/E2

Where: n: sample size, Z: (1.96), 95% confidence interval, Prevalence 20%, compared to the study of Singh HO and co-workers.[8] Error margin 10% was used. Therefore, n = (1.96) 2 x 0.2 (1 – 0.2/(0.05) 2 = 62. We sampled an extra 5% to account for possible non-response. So, the sample size in this study was 65 patients.

Age and parity variables were expressed as mean, median, standard deviation and range. We used the paired samples t-test to estimate *P*- value and *t* value. All statistical analyses were performed using SPSS software version 20 (IBM Corp) and tests of statistical significance were two-sided and differences were taken as significant when $P < 0.05$.

METHODOLOGY

After informed consent, women of the inclusion group were subjected to detailed history and thorough clinical examination.

Assessment of blood loss was done with Pictorial blood loss Assessment Chart (PBAC) score as shown in Table.1. The score of ≥ 100 suggested heavy menstrual bleeding ≥80 ml. The enrolled women were clearly given instructions to record every menstrual event according to the degree and numbers of soiling of sanitary pads of same quality of absorption each time; and number and size of passage of clots to calculate the PBAC score. [9]

Investigations like Hemoglobin(gram%), Thyroid function test (TFT), urine for pregnancy test (UPT), Trans abdominal ultrasonography (USG) to measure endometrial thickness (ET) in proliferative phase, r/o organic pathology of uterus, ovaries and cervix; endometrial biopsy if indicated (thickness >1cm) were performed. As per WHO; when hemoglobin level was below 12 gm/dl, a woman was labeled anemic.[10]

The chemical name of ormeloxifene is trans-7-methoxy-2, 2-dimethyl-3-phenyl-4 (4-(2-pyrrolidinoethoxy) phenyl (-chromanhydrochloride).[11] It competitively binds with cytosol receptors, blocks them and causes prolonged depletion resulting longer action which lasts even after withdrawal of drug. It is well absorbed from the GI tract, attains a peak level in 4 hours, and its terminal half-life is 170 hours.[12]

Women were prescribed ormeloxifene 60 mg twice a week for 3 months and called for follow-up at 3 months and the dose reduction was done to 60mg once weekly for 3 months more if drug was effective and women showed improvement of symptoms. PBAC score assessed the menstrual blood loss objectively which was correlated well with the alkaline hematin test.[13]

On 3 months post treatment follow up; PBAC score, subjective improvement of symptoms (evaluated as: no/mild/marked/aggravation of symptoms) by visual analogue scale (VAS) and side effects of drugs were noted; and the dose of ormeloxifene was reduced to half i.e. 60 milligram per week for 3 more months if the response to drug is acceptable and called for follow up at 3 months of therapy. Otherwise, women were evaluated

Table 1: Pictorial blood loss assessment chart score

A. Pads soiled with blood	Score
Light	1
Moderate	5
Saturated	20
B. Clots	**Score**
Small	1
Large	5
Flooding	5

at the end of 6 months therapy with repeat Hb%, PBAC score, trans-abdominal USG in proliferative phase for endometrial thickness measurement and subjective assessment of improvement was evaluated as: no/mild/marked/aggravation of symptoms needing alternative option of treatment.

Treatment failure was marked when there was no improvement in subjective evaluation, PBAC score >100, and those who had to undergo hysterectomy despite initial medical therapy by various route of their choice.[14]

RESULTS

During the study period, seventy women fulfilled the criteria of inclusion with PBAC score greater than 100. Out of seventy women recruited, five women were excluded from study due to lack of follow-up. So, finally sixty-five women were enrolled in the study.

Table 2 showed the clinical profile of sixty-five women offered ormeloxifene therapy. The mean age of women was 44 years, mean parity of 3, and mean duration of symptoms was 1.8 months.

There was statistically significant decrease of mean PBAC score post ormeloxifene treatment at 3rd month by 297 and at 6th month by 342 (p-value <0.05) as in Table 3. Majority of women (98.4%) recorded mean PBAC score of <100 at the end of study period despite of high PBAC score (>300) among 60% (39/65) women during recruitment.

Eighty-four percentage of women were anemic during recruitment. There was increase in hemoglobin level (mean 1.1gm/dl) after 6 months therapy, which was statistically significant. There was decrease in mean endometrial thickness (4.1mm) on trans-abdominal USG, which was also statistically significant.

Table 2: Clinical profile of women

S.No	Clinical parameter	Mean	Median	Std Deviation	Range
1.	Age(years)	44	45	4.33	35-52
2.	Parity	3	3	1.58	1-9
3.	Duration of symptoms (months)	1.8	2	0.77	1-5

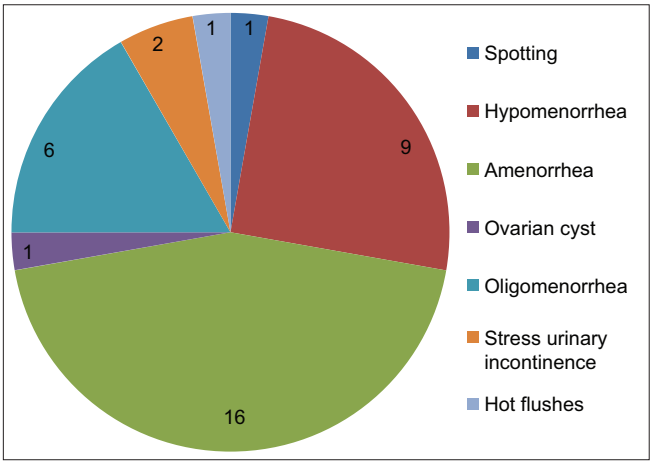
Dysmenorrhea was documented in 19% women (12/63) during recruitment and persisted in 3.18% (2/63) women after 6 months of treatment. Forty-three women (68.2%) had significant relief from passage of clots at the end of treatment (43/49).

The menstrual pattern of women became regular (50.8%), amenorrheic (25.3%), scanty (14.4%), and oligomenorrheic (9.5%) respectively after 6 months of treatment.

The subjective improvement of symptoms at 3rd and 6th month of ormeloxifene therapy was shown in Table 4. Majority (80.2%) of women witnessed marked improvement in symptoms after 6 months of ormeloxifene therapy, whereas only 71.4% had marked improvement post 3 months treatment. None of women had aggravation of symptoms with ormeloxifene.

Pie diagram 1. showed the various side effects experienced by women during ormeloxifene therapy. Amenorrhea was the commonest side effect (25.3%). None of the women stopped ormeloxifene reporting the side effects being less bothersome compared to the heavy bleeding being managed adequately.

Three women had non responsiveness to the therapy and were listed under treatment failure (4.61%). Out of them, two patients underwent hysterectomy and one woman was followed up till 6 months and counselled for alternative treatment of choice.



Pie Diagram 1: Side effects of ormeloxifene

Table 3: Outcome variables after 6 months post treatment

S. no	Outcome parameter	Pre-treatment	Post treatment (months)		t test	p-value
			3rd (n 65)	6th (n 63)		
1.	Mean PBAC score	369	72	27	14.69	p<0.05
2.	Mean Hemoglobin level (gm%)	10.6	11.7		8.92	p<0.05
3.	Mean endometrial thickness (mm)	9.9	5.8		10.01	p<0.05

Table 4: Subjective assessment of symptoms

S. No	Subjective Improvement	3 months (%)	6 months (%)
1.	No improvement	3(4.61%)	1(1.58%)
2.	Mild improvement	21(22.3%)	11(17.41%)
3.	Marked improvement	41(71.4%)	51(80.21%)
4.	Aggravation of symptoms	0	0
	Total	65	63

DISCUSSION

Many Nepalese women value uterus just for childbirth even at present dates due to ignorance. So, they afford needless hysterectomy with blind eye when any disease or disorder relating to female reproductive organ, mainly uterus; is diagnosed during menopause transition.

Heavy menstrual bleeding in the perimenopausal period without organic pathology and rules out possible causes and leave us with diagnosis of ovulatory cause for AUB (AUB-O) which was prior labeled with DUB.[15] According to ACOG, acute AUB requires immediate intervention to prevent further blood loss.[16,17] HMB interferes with women's physical, emotional, social and quality of life with or without symptoms; resulting hemorrhagic shock, anemia, iron deficiency and decrease quality of life as well as financial burden.[4] In our study, 84% of women were anemic similar to study undertaken by Gandotra et al., among thirty women with heavy menstruation.[18]

The Royal College recommends medical treatment in women with acute AUB before adopting interventional therapy like endometrial ablation (lack of technical expertise in our area) and hysterectomy (greater risk of morbidity), a last resort.[3] Ormeloxifene was found superior and safer medical therapeutic option in HMB.[12,19] Ormeloxifene was compared with oral contraceptives and progestins regarding risk of deep vein thrombosis, cardiovascular disease, obesity in the age group and better control of bleeding compared with tranexamic acid as well as reduced the need of surgical intervention from studies of Jacob and coworkers[14] (ormeloxifene vs. norethisterone), Godha et al.,[21] (ormeloxifene vs. Medroxyprogesterone acetate), Dhananjay BS et al.,[22] (ormeloxifene vs. LNG-IUS), Hymavathi K et al.,[23](Ormeloxifene vs. tranexamic acid), Arunadevi and Minnalkodi [24] (ormeloxifene vs. OCP). In our study, 60% (39/65) of women had high PBAC score (>300) during recruitment but studies conducted by Nisha et al., [25](80%,40/46) and Soniya et al.,[26](85.7%, 42/49) reported higher score compared to the current findings of the study. Ormeloxifene offered the net reduction of mean endometrial thickness of 4.1mm in our study equivalent to the result of Archana and Ritika[27] among 75 women, 4 mm in study by Hymavathi et al [23] whereas it was lesser i.e. 2.4mm and 2.7mm in studies by Jacob et al.,[14] and Gandotra et al.[18] The result of rise in mean hemoglobin level (mean) after 6months of ormeloxifene was 1.1gm/dl in our study comparing 1.3gm/dl, 1.4gm/dl and 1.3gm/dl in studies performed by Jacob et al.,[14] Nikita et al.,[18] Biswas et al.,[28] respectively.

In our study, symptomatic improvement (80%) was similar to the study of Kriplani et al [11] (88%) and Nikita et al., (76.7%).[18]

The relief of dysmenorrheal pain was extra advantage of ormeloxifene in our study and also proven by various other studies.[11,20,28] There was reduction in passage of clots from 77.7% to 9.55% which was comparable with study findings reported by Swarkar et al.,[29] (78.9% to 7.07%) at Maharashtra, India among 99 women.

Four (4.61%) percentages of women were categorized under treatment failure. Three (3.07%) percentages of women had surgical intervention in our study. The nonresponsiveness with ormeloxifene was variable from 3.3-16.7% in other studies.[25,27]

Maximum women had reported amenorrhea (25.3%) as common side effect of drug in our study which was comparable with study of Agarwal et al.,[30] which reported among 60 women (28.3%) and Kanchan et al.,[25] (32.6%) among 50 women, which was welcoming for the age near menopause, whereas it was lower incidence compared to study by Anjum S et al.,[31] (68.7%). Studies by other authors also mentioned about minor side effects not severe enough to the point of stopping ormeloxifene.[19,30]

Ormeloxifene therapy among women with AUB/DUB has been provided since 2000 and it can be started from anytime of cycle for HMB as endometrial haemostatic agent working within 48 hours of use. It is of advantage among menopause transition women being cardio-protective and prevents osteoporosis, compared to other drugs as well as budget friendly.[14] In our study, we found ormeloxifene being effective in treating HMB and high subjective improvement with acceptable side effects. The effective medical therapy has secondarily reduced the need of surgical procedures like endometrial ablation and hysterectomy.[32]

CONCLUSION

Ormeloxifene is an effective medical therapy with acceptable side effect in acute AUB with heavy menstrual bleeding in menopausal transition avoiding surgical intervention at first. So, it can be prescribed as 1st line

medical therapy in women with heavy menstrual bleeding type of acute AUB.

ACKNOWLEDGEMENT

Special thanks to Dr.Ruban Raj Joshi for supporting in sample sizing and 1st manuscript preparation, department of gynecology and radiology for the co-operation during study.

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Author's contribution:
SS- Concept, design of study, analysis, final manuscript preparation; **BT**- Review of literature, discussion, result verification; **SB-** Data entry, case collection and case follow up; **VP-** Paper work, case collection, case entry in Proforma and SPSS.

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Source of Funding: None, **Conflict of Interest:** None.