



SELECTIVE ESTROGEN RECEPTOR MODULATOR : EFFICACY IN ABNORMAL UTERINE BLEEDING IN PERIMENOPAUSAL WOMEN

Gynecology

Ankita Mani*

Senior Resident Department Of Obstetrics And Gynaecology, AIIMS, Patna
*Corresponding Author

Kanchan Sharma

Senior Resident Department Of Obstetrics And Gynaecology, AIIMS, Patna

ABSTRACT

INTRODUCTION: Abnormal uterine bleeding affects 50 % women of perimenopausal age. Ormeloxifene (SERMS) plays a sheet role in management of AUB.

OBJECTIVE: Study was focussed to see the effects of ormeloxifene on different kinds of endometrium as far as medical management of Abnormal Uterine Bleeding (AUB) is concerned.

MATERIAL & METHODS: Study was Prospective & interventional . It was done on 90 patients attending Gynae OPD Gauhati Medical College Hospital with the complain of AUB in perimenopausal age group.(37 to 48 years). They were prescribed with ormeloxifene 60mg orally twice weekly for 3 months followed by once in a week for further 3 months after doing preliminary endometrial biopsy.

RESULTS: Ormeloxifene was found to be more effective in reducing PBAC score & ET in patients with proliferative and secretory endometrium . The reduction in mean PBAC score with ormeloxifene (175.3 to 20.93)(p value 0.0001) & ET (9.6 to 2.9 mm) (p value 0.0001) in proliferative endometrium ,(179.2 to 14.8(p value 0.0001))& ET 11.1 to 1.9 mm (p value 0.0003) in secretory endometrium was observed after 6 months. However it was found ineffective in reducing PBAC score & ET in patients with atrophic endometrium . Change in PBAC SCORE from 176.4 to 150.8(p value 0.08) & in ET from 2.8 to 2.1mm(p value 0.3) was observed. No major side effects were reported.

CONCLUSION: Ormeloxifene is highly effective in AUB with proliferative and secretory endometrium in perimenopausal patients.

KEYWORDS

Abnormal uterine bleeding, perimenopausal age group, Pictorial blood loss assessment chart score (PBAC), Selective Estrogen Receptor Modulators, endometrial biopsy, ET endometrial thickness

INTRODUCTION

Any variation from normal menstrual cycle either changes in amount of blood loss, regularity and frequency of menses or duration of flow is known as abnormal uterine bleeding AUB.[1]. Most common cause of anemia in women of Reproductive age group is AUB affecting 10 to 30 percent of population .[2] 50 % women of perimenopausal age group is suffering from AUB.[3]. Around 5 % of patients with AUB attend Gynaecological OPDs(Out patient departments) for AUB but maximum have no pelvic pathology[4]. Medical management is recommended first by the RCOG (Royal college of obstetrics and Gynaecology).

The discovery that pharmacological agents can be estrogenic in some tissues while anti-estrogenic in others has led to intense interest in better understanding the mechanism by which molecular structure interact with cellular receptors to selectively affect DNA transcription in different organs. Appreciation for these selective estrogen receptor modulator (SERM's) has inevitably given way to the hope of developing one that could confer at the benefits of estrogen without any of its risk. The role of ormeloxifene (Selective estrogen receptor modulators) is the short anchor in the medical management of AUB.[5]

OBJECTIVE: The study was focussed to observe the effects of ormeloxifene in different types of endometrium as far as medical management if AUB is concerned.

MATERIAL AND METHODS

The study was prospective and interventional. It was done on 90 women attending Gynae OPD Gauhati Medical college and hospital with the complains of AUB in perimenopausal age group (37 to 48) years .

EXCLUSION CRITERIA

(1) Hypersensitivity to drugs (2) Post menopausal bleeding (3) Malignancy or atypical hyperplasia (4) cervical dysplasia (5) fibroid uterus (6) uterine size more than 6 weeks gestational pregnant uterus (7) endometrial polyp (8) Adenomyosis (9) Deranged Liver function test (10) Bleeding dyscrasia (11) History of abortion within 3 months or childbirth within 1 year After explaining regarding the study consents were taken from all the patients. Detailed history was taken . Careful clinical examination was done. The exclusion investigations were done to rule out any other cause of uterine bleeding including included complete blood cell count, thyroid stimulating hormone, coagulation profile, Pap smear, pelvic ultrasound to measure endometrial thickness and rule out any pelvic pathology and endometrial biopsy (EB) was

done to see the histopathological diagnosis .

The cases were explained to maintain a menstrual diary to record in details regarding the total number of days of bleeding, number of sanitary pads used during each cycle, degree of soaking of each pad, number and size of clots passed, and any dysmenorrhoea if experienced. Depending upon the menstrual blood loss The Pictorial Blood loss Assessment Chart (PBAC) Scoring were assessed accordingly . PBAC is a very simple procedure to assess menstrual blood loss. A PBAC score ≥ 100 indicates a menstrual blood loss ≥ 80 ml and is considered diagnostic for Heavy menstrual bleeding (HMB).[6]

The patients were managed. with ormeloxifene 60mg orally twice in a week for 3 months followed by once in a week for further 3 months. The cases were followed up after one month , 3 month and 6 months respectively. During the visit detailed menstrual history were taken to calculate PBAC score. Hb concentration & endometrial thickness were measured as well. Side effects experienced , if any were also taken into consideration.

Statistical Analysis Data were compared using Mann-Whitney U test for numerical variables and Fischer's exact test for categorical variables. A P value < 0.05 was considered significant. Friedman's ANOVA followed by Dunn's posthoc test was used for multiple comparisons in PBAC scores, Hb level & endometrial thickness.

RESULTS

In the present study, majority of the cases 45 patients (50%) are in the age group of 41-44 years as shown in table 2.

Maximum no. of patients 45 (50%) were having proliferative endometrial hyperplasia. 30 (33%) were having secretory endometrium. Atrophic endometrium was seen in 15 (17%) patients as shown in table 3.

ormeloxifene was found to reduce PBAC score significantly in both proliferative endometrium & secretory endometrium from 175.3 to 51.2(p value 0.0001) after 3 months & to 20.9(p value 0.0001) after 6 months in proliferative endometrium and from 179.2 to 48.4(p value 0.0001) and 14.8(p value 0.0001) after 3 & 6 months respectively in secretory endometrium as shown in table 4 & Graph 1.

However in patients with atrophic endometrium initially the mean PBAC score was reduced just from 176.4 to 144.2 after 3 months of treatment (p value 0.09) but again the PBAC score increased upto

150.8 after 6 months of therapy (p value 0.08) suggesting that ormeloxifene is not as effective in reducing PBAC score in cases with atrophic endometrium.

Change in Hb level in proliferative endometrium increased from 9.1gm/dl to 10.4gm/dl (p value 0.0001) after 3 months & up to 11.1gm/dl (p value 0.0001) after 6 months of treatment. In case of secretory endometrium Hb level increased from 8.9gm/dl to 10.5 gm/dl (p value 0.0001) after 3 months & to 10.9gm/dl (p value 0.0004) after 6 months respectively (table 5 & graph 2) However in atrophic endometrium cases Hb level increased slightly from 7.8gm/dl to 8.3gm/dl (p value 0.5) after 3 months of treatment but again decreased to 6.8gm/dl (p value 0.6) after 6 months of treatment with ormeloxifene.

Ormeloxifene was also found to be effective in reducing endometrial thickness in both proliferative endometrium from 9.6 to 4.2mm (p value 0.0001) after 3 months and 2.9mm (p value 0.0001) after 6 months and in secretory endometrium from 11.1 to 2.1 mm (p value 0.0005) and 1.9mm (p value 0.0003) after 3 & 6 months of treatment respectively as shown in table 6 & Graph 3.

However in atrophic endometrium cases ET was not reduced considerably. Reduction of ET from 2.8mm to 2.3mm after 3 months (p value 0.7) & 2.1mm after 6 months (p value 0.34) suggest that ormeloxifene is not effective in reduction of ET in patients with atrophic endometrium. Last but not the least no major side effects were

noted.

TABLES AND GRAPHS

Table 1: PBAC scoring

PADS	
Lightly soiled pads	1
Moderately soiled pads	5
Severely soiled pads	20
Clots	
Small clots	1
Large clots	5
Flooding	20

Table 2: showing clinical profile of women

Age in Years	No. of cases	Percentage%
37-40	18	20
41-44	47	50
45-48	27	30

Table 3 showing distribution of the patients as per pre treatment endometrial histopathology

D & C REPORT	Cases	PERCENTAGE%
Proliferative endometrium	45	50
Secretory endometrium	30	33
Atrophic endometrium	15	17

Table 4 showing relation between D&C findings & PBAC score

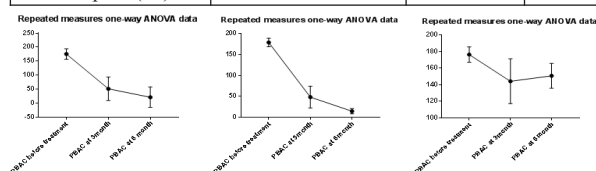
D & C endometrium	Mean Pre-treatment PBAC SCORE	Mean PBAC SCORE at 3rd month PBAC3	Mean PBAC SCORE at 6th month PBAC6	Mean difference b/w PBAC3-PBAC0	P value	Mean difference b/w PBAC6-PBAC0	P value
Proliferative (45)	175.3	51.2	20.9	124.1	0.0001	154.4	0.0001
Secretory (30)	179.2	48.4	14.8	130.8	0.0001	164.4	0.0001
Atrophic (15)	176.4	144.2	150.8	32.2	0.09	25.6	0.08

Table 5 showing relation between D&C findings & Hb level

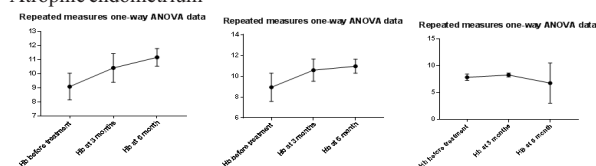
D & C Endometrium	Mean Pre-treatment Hb level	Mean Hb at 3 rd month	Mean Hb at 6 th month	Mean difference b/w Hb ₃ -Hb ₀	P value	Mean difference b/w Hb ₆ -Hb ₀	P value
Proliferative (45)	9.1	10.4	11.1	1.32	0.0001	2.06	0.0001
Secretory (30)	8.9	10.6	10.9	1.65	0.0001	2.03	0.0004
Atrophic (15)	7.9	8.3	6.9	0.42	0.5	1.08	0.6

Table 6 showing relation between D&C findings & ET

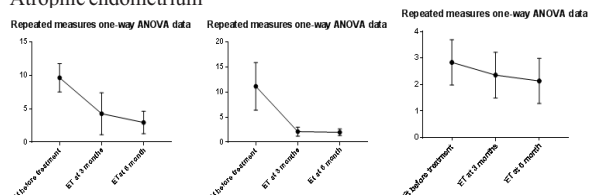
D & C Endometrium	Mean Pre-treatment ET	Mean ET at 3 rd month	Mean ET at 6 th month	Mean difference b/w ET ₃ -ET ₀	P value	Mean difference b/w ET ₆ -ET ₀	P value
Proliferative (45)	9.6	4.3	2.9	5.4	0.0001	6.6	0.0001
Secretory (30)	11.1	2.1	1.9	9.01	0.0005	9.14	0.0003
Atrophic (15)	2.8	2.4	2.1	0.48	0.7	0.7	0.3



Proliferative endometrium
Secretory endometrium
Atrophic endometrium



Proliferative endometrium
Secretory endometrium
Atrophic endometrium



Proliferative endometrium
Secretory endometrium
Atrophic endometrium

DISCUSSION

Present Study is a prospective study to evaluate the effects of ormeloxifene on menstrual blood loss & side effects as well. The aim of the study is to compare the therapeutic efficacy of ormeloxifene in AUB in women of perimenopausal age group in relation to different kinds of endometrium.

Maximum no. of patients i.e. 45 (50%) were of age group 41 to 44 years. Jacob K J et al [7] & S fayyaz et al.; [8] also have maximum no. of patients between age group 40 to 50.

Ormeloxifene competes with estradiol for binding with cytosol receptors. It not only blocks cytosol receptors but also causes their prolonged depletion and has long lasting post withdrawal effect. Thus efficacy of the drug improves with time which is depicted by increasing reduction in menstrual blood loss with prolonged use. The results in our study with respect to efficacy of ormeloxifene in reducing MBL were comparable with majority of the other similar studies.

BelladGirija et al.; [9], Grover S et al.; [10], Ravibandu&Palla et al.; [11] and Agarwal and Singh et al.; [12], Biswas et al.; [13] & Tapan et al.; [14] all found significant increase in Hb level similar to present study where significant rise in Hb level is seen in proliferative & secretory endometrium. However no significant rise in Hb level seen in atrophic

endometrium is seen in present study.

Mandal et al [15] ; Tripura et al [16]; Dhananjay et al [17] & others found a significant decrease in ET with ormeloxifene therapy. The findings are similar to present study where ormeloxifene caused a significant decrease in ET in proliferative & secretory endometrium. However, no significant change in ET is seen in atrophic endometrium.

Kriplani et al ; [18]; Dadich et al [19] & others found significant reduction in PBAC score similar to present study. However it was found that ormeloxifene is ineffective in reducing PBAC score in patients with atrophic endometrium (ET < 5mm) in 100% of cases. The finding is similar to Shrivage et al.; [20] in which 80 % of the patients who failed to respond to ormeloxifene had ET < 5mm (atrophic endometrium). As per Shia Salen" criteria cut off value to diagnose atrophic endometrium was taken as 5 mm.

Limitations of the study

It is a short duration study with the absence of double blinded placebo controlled trial to control information bias. Long-term follow-up is required to observe the efficacy of these drugs and to note the recurrence of symptoms.

CONCLUSION

Abnormal uterine bleeding is one of the chief complain of women of perimenopausal age group. Ormeloxifene is found to be effective in treating these cases as assessed by reduction in PBAC score in proliferative and secretory endometrium. But it is found not to be as effective in treating AUB with atrophic endometrium.

Due to its low cost and convenient dose schedule it has comparatively a very good compliance. Thus, Ormeloxifene should be considered for the medical management of idiopathic Heavy menstrual bleeding in perimenopausal patients.

ACKNOWLEDGEMENT

I express my profound sense of gratitude and gratefulness to my teacher Dr. RK Talukdar for guiding me. I express my heartfelt thanks to Dr. Arun Kumar & Dr. Kanchan for providing technical support. A very special thanks to Dr. Amit Kumar for being a source of inspiration.

REFERENCES

1. Bhatia N. Abnormal and Excessive Uterine Bleeding. In Neeraj Bhatia editor. Jeffcoate's Principles of Gynaecology. 5th Edition. London: Arnold Publishers; 2001. p.560
2. Fleischer AC, Kaleris GC, Entman SS. Sonographic depiction of the endometrium during normal cycles. *Ultrasound in medicine & biology*. 1986 Apr 1; 12(4):271-7.
3. Prentice A. When does heavy flow merit treatment? *The Practitioner*. 2000 Mar; 244(1608):174.
4. Fraser IS. Treatment of ovulatory and anovulatory dysfunctional uterine bleeding with oral progestogen. *Australian and New Zealand Journal of Obstetrics and Gynaecology*. 1990 Nov 1; 30(4):353-6.
5. Kriplani A, Kulshrestha V, Agarwal N. Efficacy and safety of ormeloxifene in the management of menorrhagia: A pilot study. *The journal of obstetrics and gynecol research* 2009; 35 (4): 746–52
6. HIGHAM JM, O'Brien PM, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *BJOG: An International Journal of Obstetrics & Gynaecology*. 1990 Aug 1; 97(8):734-9.
7. A comparative study on the effectiveness of ormeloxifene versus norethisterone in the management of perimenopausal dysfunctional uterine bleeding(Deepak AV. *IAIM*, 2015; 2(7): 87-92
8. Mandal D ,Parmanik S. Comparative Study of Ormeloxifene verses OCPs in management of DUB. *International Journal of Health & Allied Sciences* • Vol. 3 • Issue 4 • Oct-Dec 2014
9. Shahab P, Jain S, Jain P, Jain U. Ormeloxifene boon to perimenopausal DUB women in avoiding hysterectomies. *International journal of medical science and education*. 2014; 1(1).
10. BelladGirija C, Lakshmi KS. Ormeloxifene in the Management of Dub. *Journal of Evidence based Medicine and Healthcare*. 2015; 2(37):6125-6131.
11. Grover S, Chhabra A, Sainath B. A Study of Ormeloxifene in case of Dysfunctional uterine bleeding. *International Journal of Medical and Dental Sciences*. 2013; 1(2):162-9.
12. Ravibandu K ,Palla J ,Chintada G S. A Study of Efficacy of Ormeloxifene in the Pharmacological Management of Dysfunctional Uterine Bleeding *Journal of clinical and diagnostic research* Volume 7(11); 2013 Nov
13. Agarwal N, Singh S, Singh S, Agarwal M, Manocha P. Comparative evaluation of the efficacy and safety of ormeloxifene and norethisterone in dysfunctional uterine bleeding. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*. 2013; 2(2):194-8.
14. Biswas SC, Saha SK, Bag TS, Ghosh Ray SC. Ormeloxifene - A Selective Oestrogen Receptor Modulator for treatment of Dysfunctional Menorrhagia. *Journal of Obstetric Gynaecology* 2004; 54 (1):56-9
15. Bhattacharyya. Tk, Banerji. A. Efficiency of a selective estrogen receptor modulator ormeloxifene in management of dysfunctional uterine bleeding.
16. Mandal D ,Parmanik S. Comparative Study of Ormeloxifene verses OCPs in management of DUB. *International Journal of Health & Allied Sciences* • Vol. 3 • Issue 4 • Oct-Dec 2014
17. Tripura M, Srilakshmi B. Ormeloxifene in management of DUB; *J. Obstet Gynaecol Res*. vol. 35, No. 4: 746–752, August 2009

18. Dhananjay BS, Nanda SK. Role of sevista in management of uterine bleeding. *Journal of clinical diagnostic and Research* 2013; 7 (1): 132-34
19. Kriplani A, Kulshrestha B, Agarwal N. Efficiency and safety of ormeloxifene in management of menarhagia: a pilot study. *J obstet Gynecol Res* 2009; 35: 746-5
20. Dadich, S, Agarwal, M, Soni and R. Jain. Role of ormeloxifene in medical management of dysfunctional uterine bleeding. *Asian journal of Obs and Gynae Practice*. 2012; 6: 28-31
21. Shrivage J, Mekhala D, Bellad MB Ormeloxifene vs MPA in treatment of DUB. *Journal of South Asian Federation of Obstetrics and Gynaecology*. 2011; 3(1):21-24