CLINICAL PRACTICE

Efficacy of a Selective Estrogen Receptor Modulator: 'Ormeloxifene' in Management of Dysfunctional Uterine Bleeding

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Abstract

Background: Ormeloxifene, a third generation selective estrogen receptor modulator, has been claimed to ameliorate symptoms of DUB. This study was undertaken to compare the efficacy of ormeloxifene and norethisterone.

Methods: 180 cases of DUB, who have completed child bearing and are above 35 years, were randomly assigned ormeloxifene, progesterone and iron groups. Ormeloxifene group received ormeloxifene for 12 weeks. Norethisterone group received norethisterone for 12 days in every cycle for six cycles. Iron was given as 60 mg of elemental iron daily. Before starting drug therapy, ultrasound, office hysteroscopy and endometrium sampling for histopathology was obtained and repeated at end of follow-up. The side effects and complications of drug ormeloxifene were noted and relief of symptoms and patient acceptability were compared with norethisterone.

Results: 81.7% in the ormeloxifene administered subjects marked relief of symptoms with significant reduction of PBAC scores, reduction of blood clots, and rise in hemoglobin levels. Side effects/complications included amenorrhea, urinary incontinence and genital prolapse. The ease of administration of ormeloxifene facilitated compliance and acceptability.

Conclusion: Ormeloxifene is superior to norethisterone in the management of DUB and may be prescribed as a first line treatment to women, who have completed child bearing.

Keywords: SERM, Dysfunctional uterine bleeding, Norethisterone.

INTRODUCTION

In western countries, 28% of women consider their menstruation as excessive and nearly 10% of employed women will need to take leave from work because of menorrhagia.[1] Over 75,000 hysterectomies are carried out every year with 30% of them for menstrual disturbances.[2] Over the years, menorrhagia has become quite common presenting complaint. Today the total span of menstruating years has increased due to early menarche and late menopause and women are increasingly unwilling to accept menstrual problems. The ultimate cure is hysterectomy. Though the option is relatively safe with low mortality, one cannot deny the morbidity associated with this modality of treatment. In recent years, concern has been expressed about possible long-term complications of hysterectomy like premature ovarian failure, cardiovascular disease and intestinal or urinary dysfunction. Thus, more and more women are looking forward to an effective medical therapy. Antifibrinolytics, nonsteroidal anti-inflammatory drugs, progesterones, danazol, gonadotropin releasing hormone analogues and levonorgestrel—releasing intrauterine system have all been used with varying results. The most commonly used drug, however, are the progesterone and norethisterone. Recent studies doubt its effectivity in reducing blood loss.[3] Ormeloxifene, a third generation selective estrogen receptor modulator (SERM) selectively acts on estrogen receptors as estrogen antagonist and agonist in certain reproductive tissues. The effect of this SERM on the vascular endothelium leads to decrease in blood loss and thereby amelioration of symptoms in dysfunctional uterine bleeding (DUB). With this background, the present study was undertaken to study the efficacy or ormeloxifene and compare with the most commonly used drug norethisterone in the treatment of DUB. We also studied the effect of drug on the endometrium and side effects besides patient's acceptability and compliance.

MATERIALS AND METHODS

The prospective analytical study was carried out at tertiary care hospital attached with medical college over a period of two years. Patients with DUB over the age of 35 years were included in the present study. Those with history of abortion within 3 months, or childbirth within 1 year or those desirous of future pregnancy were excluded. Likewise IUCD or pill users or those

with autoimmune diseases, diabetes, thyroid, liver or coagulation disorders or those with congenital anomaly of uterus were also excluded.

A total of 180 consecutive cases of DUB fulfilling the inclusion and exclusion criteria were initially selected. The subjects were randomly assigned into the progesterone (P) group, ormeloxifene (O) group and iron (I) groups. The latter was included to negate the beneficial effect of iron, if any, as iron was routinely supplemented to all cases of DUB. The 'O' group received ormeloxifene 60 mg twice a week for 12 weeks followed by once a week for next 12 weeks. The 'P' group received norethisterone 10 mg daily for 12 days in every cycle from 14th day of cycle for 6 cycles. 'I' group received tablet (tab) ferrisulphate 200 mg containing 60 mg of elemental iron 1 tablet daily only. 17 patients in the progesterone group and 1 in the ormeloxifene group opted out of the study. Fresh 18 cases were recruited into these groups.

Initial evaluation was carried out, and systemic diseases, coagulation, liver disorders, diabetes mellitus and thyroid dysfunction were excluded. A detailed gynecological examination excluded any uterine pathology. Ultrasound and office hysteroscopy were done to rule out any congenital malformation and other organic causes for abnormal uterine bleeding. Before starting drug therapy, endometrium was obtained for histopathology and sampling repeated after a course of drug at 9 months.

Endometrial thickness (ET) using transvaginal sonography (TVS) was carried out every 3 months to study response of the endometrium to the drug. The side effects and complications of the newer drug ormeloxifene were noted and relief of symptoms and patient acceptability were compared with norethisterone. All patients were followed up till 9 months of commencement of the treatment.

Pictorial blood loss assessment chart (PBAC) was used to measure the menstrual blood loss (MBL). The women were asked to use certain sanitary napkins which have similar absorbent capacities. They recorded the number of napkins used each day and the degree of soiling of each pad used. Number and sizes of clots passed were also noted. Scores were assigned to different degrees of soiling of sanitary napkins and number and size of clots passed. A PBAC score of greater than or equal to 100 was considered diagnostic of menorrhagia. The main outcome measures were MBL, passage of clots, blood hemoglobin(Hb) level and ET in proliferative phase by TVS. Anova was carried out to check the homogeneity between the groups pretreatment with respect to PBAC score, Hb and ET values and it was found to be not significant ($p > 0.05$), that is, the groups were similar before starting the treatment.

OBSERVATIONS AND RESULTS

The improvement in symptoms was assessed both subjectively as well as objectively by noting the pretreatment and post-treatment PBAC scores. Subjective analysis was carried out by asking the patients whether they felt mild, marked, no improvement or worsening of symptoms. 81.67% of patients in 'O' group felt marked improvement of symptoms compared to 35% in 'P' group and 11.67% in the 'I' group (Table 1).

DESCRIPTIVE STATISTICS WITH RESPECT TO ALL THE THREE GROUPS

The descriptive statistics of pre- and post-PBAC, endometrial thickness (ET) and hemoglobin (Hb) levels before and after treatment in all the three groups is reflected in Tables 2 to 4. To test whether there was any significant difference between the pre and post values with respect to the variables, PBAC, ET and Hb paired t-test was carried out in all three treatment groups.

Table 1: Subjective improvements in all groups

Improvement	*I group*	*O group*	*P group*
Mild	8 (13.33%)	–	8 (13.33%)
Marked	7 (11.67%)	49 (81.67%)	21 (35%)
No improvement	44 (73.33%)	10 (16.67%)	29 (48.33%)
Worsened	1 (1.67%)	1 (1.67%)	2 (3.33%)
Total	60	60	60

Table 2: For 'I' group

Variable	*n*	*Minimum*	*Maximum*	*Mean*	*Standard deviation*
PBAC (pre)	60	12.0	146.0	107.73	32.04
PBAC (post)		14.0	138.0	100.87	32.10
ET(pre)	60	3.8	8.2	6.27	1.03
ET(post)		3.7	7.2	5.79	0.689
Hb(pre)	60	6.8	11.8	8.71	0.898
Hb(post)		7.9	11.9	9.28	1.040

Table 3: For 'O' group

Variable	*n*	*Minimum*	*Maximum*	*Mean*	*Standard deviation*
PBAC (pre)	60	16.0	142.0	108.70	30.44
PBAC(post)		0	118.0	62.48	28.91
ET(pre)	60	3.8	11.5	6.515	1.614
ET(post)		0.0	8.0	5.357	1.456
Hb (pre)	60	3.8	11.8	8.49	1.642
Hb(post)		8.0	13.0	11.028	0.933

Table 4: For 'P' Group

Variable	*n*	*Minimum*	*Maximum*	*Mean*	*Standard deviation*
PBAC (pre)	60	14.0	142.0	113.87	25.74
PBAC (post)		16.0	132.0	94.07	25.91
ET(pre)	60	4.1	9.3	6.52	1.105
ET(post)		3.2	7.8	5.86	0.874
Hb(pre)	60	6.2	12.1	8.710	0.972
Hb(post)		7.8	12.1	9.803	1.078

PBAC Score

Pre- and post-treatment values differed statistically significantly ($p < 0.05$) in all three groups. PBAC score reduced after the drug administration in all the groups and the scores reduced maximally in the 'O' group followed by 'P' group and then 'I' group.

ET

From the analysis, it is revealed that the pre and post values differed significantly ($p < 0.05$) in all three groups for endometrial thickness. It reduced after the drug administration in all three groups.

Clots

The proportion of subjects, who had reduction with respect to clots after administration of drug, was also assessed. The reduction in clots in 'O' group was 91.18% as compared to 14.28% and 42.86% in the 'I' and 'P' groups respectively. This proportion was statistically significant ($p = 0.000$) with maximum reduction in 'O' group.

Hb Level

Analysis of Hb levels shows that the pre and post values differ significantly ($p < 0.05$) again in all three groups. The Hb levels increased in all three groups after the drug administration and the level increased maximum in those patients, who were given ormeloxifene followed by 'P' group and then 'I' group.

Hysteroscopy Findings

When the hysteroscopy findings were compared in all the three groups, it was found that in the 'I' group, 3 cases worsened vis-à-vis 5 cases in 'P' group in the form of development of endometrial polyps. In the 'O' group, there was no deterioration in any of the cases.

The proportion of cases that had improved hysteroscopy findings in the form of thinning of endometrium was also analyzed. 94.74% in 'O' group improved as against 47.73% in 'P' group and this proportion was statistically significant ($p = 0.000$). Group 'I' showed no improvement.

Evaluation of the endometrial histopathology pre- and post-therapy shows maximum number of simple endometrial hyperplasia post-therapy in the 'I' group (total of 9 cases) followed by 6 cases in the 'P' group and only 4 cases in the 'O' group.

Complication for All Groups

The only adverse effect in the 'I' group was spotting. The complications of 'O' group is shown in Table 5. It is pertinent to note that 3 patients developed stress urinary incontinence (SUI) and 3 developed genital prolapse after completion of the course of therapy and were detected during follow-up at the end of 9 months. All these patients were in the perimenopausal age group. Like the 'I' group the only side effect in the 'P' group was spotting/breakthrough bleeding.

17 patients were excluded from the present study in the 'P' group as they found symptoms of bloating, mastalgia unbearable and opted out of the study within the first 2 cycles of treatment. 1 patient opted out in the 'O' group without any obvious reason after the first 4 weeks of treatment. Since these patients did not complete the drug schedule, they were excluded and fresh patients were recruited in their place.

There were 7 cases of amenorrhea and 1 case of hypomenorrhea in the 'O' group in stark contrast to the 'P' and 'I' groups, which had no such complications. These complications turned out to be desirable as they occurred in the perimenopausal age group and was welcomed by this subset of patients (Table 6).

DISCUSSION

The traditional surgical treatment for menorrhagia is hysterectomy. While hysterectomy offers an effective cure, it is suitable only for those, who have no further wish to conceive. The procedure involves major surgery with significant postoperative morbidity.[4,5] Endometrial ablation techniques

Table 6: Complications: Drug group 'O' (n = 11)

Complications	*Frequency*	*Percent*	*95% CI*	
Amenorrhea	7	63.63	33.64	87.21
Spotting	1	9.1	0.2	41.3
Hypomenorrhea	1	9.1	0.2	41.3
SUI	3	27.27	3.17	48.27
Prolapse	3	27.27	7.45	57.81

Table 5: Complications amongst all groups

Complications	*Freq. 'P'*	*Percent*	*Freq. 'O'*	*Percent*	*Freq. 'I'*	*Percent*
Third degree prolapse with SUI and amenorrhea	0	0.0	1	9.1	0	0.0
Amenorrhea	0	0.0	4	36.4	0	0.0
Breakthrough bleeding	1	12.5	0	0.0	0	0.0
Hypomenorrhea	0	0.0	1	9.1	0	0.0
Spotting	7	87.5	1	9.1	1	100.0
SUI	0	0.0	2	18.2	0	0.0
UV prolapse and amenorrhea	0	0.0	2	18.2	0	0.0
Total	8	100.0	11	100.0	1	100.0

offer an alternative surgical treatment option with significantly reduced postoperative morbidity.[5-7] They may be unsuitable for women wishing to retain their menstrual or reproductive function and require technical expertise not routinely available. For women, who have not completed their family or who are unfit or unwilling to undergo surgery, or those keen to maintain their menstrual or reproductive function, medical therapy represents the only viable option.

Ormeloxifene is a benzopyran SERM, which blocks the cytosol receptors by its competitive binding over estradiol. It has mild estrogenic activity on vagina, bone mineral density, CNS and lipids.[8] The drug is primarily a potent estrogen antagonist but also has a weak agonist activity in selected tissues. The drug demonstrates a suppressive or a stimulatory effect on gonadotropin release. Such antiestrogens are expected to exert contraceptive effects. It normalizes the bleeding from uterine cavity by regularizing the expression of estrogen receptors on the endometrium and, hence the drug was tried in patients of DUB. It is also a potent antiproliferative agent in breast tissue. Chronic use upto 4 years has shown no evidence of common, serious adverse events and no serious ovarian pathology. Additional benefit of this drug is that it decreases total cholesterol, LDL cholesterol by about 20 to 30%. The drug is known to increase ET significantly without proliferation.[9]

It is usually hard to quantify MBL objectively. As a consequence, menorrhagia is defined subjectively in clinical practice. We opted to use PBAC chart as used by Higham et al.[10] It is a simple and less time consuming procedure, which does not require collection of sanitary products and avoids costly chemical assay. The patients in this study comprised all types of DUB. There was improvement with all categories of drugs though the extent or degree of improvement varied in the cases of menorrhagia. Ormeloxifene was definitely superior as compared to progesterone or iron. DUB not associated with excessive blood loss was also treated and included in the present study though we focused on the menorrhagic cases for evaluating efficacy of therapy.

Cameron et al in 1987[11] showed that short-term progestogen therapy caused a non-significant reduction in MBL from 131 to 110 ml in 6 women with ovulatory menorrhagia after the treatment with norethisterone 5 mg bd from day 16 to 26 of the cycle. Further work on a regimen using the same dosage from day 19 to 26 of the cycle in 15 women with ovulatory menorrhagia showed a 20% reduction in MBL from 109 to 92 ml, but two-thirds of patients thus treated had post-treatment MBL >80 ml (Cameron et al 1990).[12] Preston et al in 1995 using norethisterone 5 mg bd from day 19 to 26 of the cycle in 21 women with confirmed ovulatory menorrhagia demonstrated a 20% increase in MBL.[3] Increasing the length of treatment to 21 days, each cycle showed improved results in one small study involving 10 patients with proven ovulatory menorrhagia (Fraser 1990).[13] Our results with a shorter duration of progestogen are at variance with that of Preston et al 1995,[3] but in agreement to the findings of Fraser, 1990[13] and Irvine et al 1998.[14] A shorter duration of progestogen from days 12 to 26 of the cycle has proven to be effective and gave a 50% reduction in MBL in 6 patients with confirmed anovulatory menorrhagia with all but one post-treatment MBL being below 80 ml (Fraser, 1990).[13] However, short-duration progestogens are ineffective for the majority of patients, who present with ovulatory menorrhagia. In our study, the PBAC score in the 'P' group fell from the mean value of 113.87 to 94.07 and the improvement was statistically significant.

Studies on the use of ormeloxifene for DUB are limited. Scanning the literature revealed only a single study by Biswas et al in 2004[15] on the efficacy of ormeloxifene in the treatment of DUB. The present study revealed a significant improvement of patient's condition in the ormeloxifene treated group both subjectively and objectively. 81.67% of patients in this group showed marked improvement of symptoms. The mean PBAC score fell from 108.70 to 62.48. Hb level too rose from 8.49 gm % to 11.03 gm%. Presence of clots, an obvious evidence of excessive menstrual flow, was maximally reduced in the ormeloxifene group. The finding of the post-treatment hysteroscopic assessment of the uterus in the form of endometrial thickness and development of endometrial polyps was also more favorable in the ormeloxifene group. The results of the present study are comparable to study by Biswas et al.[15] Seven of our perimenopausal patients in the ormeloxifene group developed side effect of amenorrhea, which was highly acceptable in this age group of patients. The adverse effect of SUI in 3 patients and genital prolapse in 3 patients with ormeloxifene, were not encountered in the P group. Similar side effects were also noticed by Goldstein et al[16] and Hendrix et al. We observed these side effects only in the perimenopausal age group. A larger study to validate these deleterious side effects is required. These side effects apart, ormeloxifene has been found to have a favorable effect on the lipid profile,[9] which again is a favorable aspect in patients in the relatively elderly age group.

CONCLUSION

Both ormeloxifene and norethisterone significantly reduce blood loss in patients of DUB evidenced by decrease of PBAC score, reduction of passage of blood clots during menstruation and rise in hemoglobin levels. Ormeloxifene was found to be superior to norethisterone in reducing the menstrual blood loss. Amenorrhea/hypomenorrhea with the use of ormeloxifene were a desirable side effect in the perimenopausal age group in which they were detected. The serious side effects of SUI and genital prolapse encountered in this group require further validation before the drug can be recommended routinely for treatment in this age group.

The ease of administration of the drug facilitates patient compliance and acceptability and the marked relief of symptoms results in higher clientele satisfaction. Ormeloxifene should be the drug of choice in patients of DUB, who have completed their child bearing but used cautiously after counseling in the perimenopausal age group.

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