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Ormeloxifene A Selective Estrogen Receptor Modulator, For Treatment Of Dysfunctional Menorrhagia

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OBJECTIVE - To evaluate the efficacy of Ormeloxifene for dysfunctional menorrhagia (DUB). **METHODS** - Eighty five women aged 30 to 51 years who attended the outpatient gynecology department with complaint of heavy menstrual flow were recruited for the study. Ormeloxifene (60 mg)was given orally twice a week for first 12 weeks and then once a week for up to next 12 weeks. Menstrual blood loss measurements using pictorial blood loss assessment chart (PBAC), blood hemoglobin (gm/dl) levels and endometrial thickness were the main measurements to evaluate the efficacy of therapy. Statistical analysis was done using a paired 't' test and 'z' test. **RESULTS** - The median difference between pretreatment and post-treatment PBAC score of 97.2 was statistically significant (P<0.001). The difference in mean hemoglobin concentration of 1.31 gm/dl between pretreatment and post-treatment levels was also statistically significant (P<0.001, 95% CI= 0.389 to 2.23). Seventy four out of 85 subjects (87.05%) showed a reduction in endometrial thickness as assessed by trans vaginal sonography(TVS). Only se out of 85 (8.2%) women needed hysterectomy. **CONCLUSION** - Because of convenient dosage schedule and higher cost-benefit ratio, ormeloxifene is an effective drug therapy in dysfunctional menorrhagia.

Key words - ormeloxifene, SERM, menorrhagia

Introduction

Menorrhagia, (menstrual blood loss > 80 ml per cycle), affects 10 to 33% of women at some stage in their lives[1,2,3]. In majority of the cases there is no organic disease and the bleeding is termed dysfunctional or essential. Despite the recent development of a less invasive surgical approach viz. endometrial ablation, the traditional hysterectomy is still the only suitable definitive therapy for those who have no further wish to conceive[4]. There continues to be a demand for alternative to surgery as a means of reducing menstrual blood loss.

Medical management of menorrhagia is a challenging task and wide variations in the available drugs prescribed for this condition show a lack of consensus for medical treatment[4,5]. Selective estrogen receptor modulators (SERM) are a new category of therapeutic agents that selectively bind with high affinity to estrogen receptors (ER) and mimic the effect of estrogen in some tissues but act as estrogen antagonists in others.

Ormeloxifene, one of the SERMs, mediates its effects by high affinity interaction with ER, antagonizing the effect of estrogen on uterine and breast tissue and stimulating. Its effect on vagina, bone, cardiovascular system and central nervous system. It is therefore, suitable in the treatment of heavy dysfunctional uterine bleeding (DUB).

The purpose of the present study was to evaluate the efficacy of ormeloxifene in women with essential or dysfunctional menorrhagia.

Materials and Methods

The research project approved by the ethical committee, studied the effect of ormeloxifene (Sevista®, Torrent Pharmaceuticals Ltd.) on heavy menstrual blood flow. Two pretreatment baseline cycles were compared to three to six consecutive treatment cycles of ormeloxifene. The drug was administered orally in the form of tablet (60 mg) twice a week, every Sunday and Wednesday for the first 12 weeks and then once a week for another 12 weeks, if required.

Subjects were recruited at random from outpatient department of Obstetrics and Gynecology, between May 2001 to June 2002. Women aged 30 to 51 years with the diagnosis of DUB, with cycle length of 24 to 35 days were selected for the study. They were advised to attend

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four weekly or earlier if needed. Exclusion criteria were presence of any pelvic pathology such as uterine fibroids, systemic disease such as platelet disorder or coagulopathy, previous history of thrombosis, pregnancy and consistent use of oral contraceptives or non-steroidal anti-inflammatory agents. The women were multiparous (para 1 to 6), who did not wish to conceive further and had no clinical evidence of jaundice or hepatic dysfunction, polycystic ovarian disease, cervical hyperplasia, chronic cervicities and hypersensitivity to the drug. Informed written consent was obtained.

The main outcome measures were menstrual blood loss, blood hemoglobin levels and endometrial thickness in proliferative phase as studied by trans-vaginal sonography (TVS).

Pictorial blood loss assessment chart (PBAC)[9], a method that correlates well with the alkaline hematin test[7] was used to measure the menstrual blood loss (MBL). The women were asked to use certain sanitary napkins which have been shown to have similar absorbent capacities. They recorded the number of napkins used each day and the degree of soiling of each pad used. Number and size of clots passed were also noted. Scores were assigned to different degrees of soiling of sanitary napkins and number and size of clots passed (Table I). A PBAC score of greater than or equal to 100 was considered a menstrual blood loss greater or equal to 80 ml and was considered diagnostic of menorrhagia[9].

Blood hemoglobin (g/dl) and endometrial thickness by TVS were measured initially and at the end of the study. A well designed questionnaire recorded the subjective assessment of menstrual flow and dysmenorrhoea and/or any side effects of the drugs. Menstrual flow was categorized as light, normal or average, heavy and flooding. Dysmenorrhea was categorized as absent, mild, moderate and severe.

Results

Table I shows that eighty five women recruited in the study had objective evidence of menorrhagia by an average PBAC score of greater than or equal to 100 over the pretreatment cycles.The average age and parity were 39.2 (range 31 to 51) years and 2.4 (range 1 to 6) respectively.

Table II shows the different outcome measurements. The median pretreatment baseline PBAC score was 272.0 with a range of 123 to 865. The median post treatment PBAC score was 107.8 with a range of 60.7 to 415. Sixty one out of 85 patients (71.76%) recorded a mean PBAC score of less than 100 at the end of study. It was more marked in the age group of above 40 years i.e., 32 out of 39 subjects(82.05%).

Fifty five patients had anemia upon entry into the study as defined by WHO standards [hemoglobin (Hb) < 12 g/dl]. Thirty five had significant anemia of Hb level less than 10 g/dl. The mean pretreatment Hb concentration was 9.42 g/dl with a range of 7.85 to 11.42 g/dl. The mean post treatment Hb concentration was 10.73 g/dl with a range of 9.2 to 12.57 g/dl. The mean increase of 1.31 in Hb concentration was statistically significant ($P < 0.001$, paired $t = 25.7$, 95% CI = 0.389 to 2.23) (Table II).

Seventy four out of 85 patients (87.05%) showed reduction in endometrial thickness as measured by TVS in the proliferative phase. Fifteen subjects (17.64%) who developed amenorrhoea had atrophic endometrium (less than 5 mm thickness).The reduction in endometrial thickness was statistically significant.

Eleven women who continued to have heavy flow were subjected to dilatation and curettage followed by histopathological study. Three women showed atypical endometrial hyperplasia, four had proliferative, endometrium and four had secretory endometrium. The four with proliferative endometrium were switched over to progestogen (medroxyprogesterone acetate). The seven with atypical or secretory endometrium were subjected to total hysterectomy, the incidence of hysterectomy being 8.2% (7/85) in the series.

Table III shows reasonable improvement in amount of flow assessed subjectively by the drug users, though 15 patients developed amenorrhoea.

Table I. PBAC Scoring

Pads	Lightly soiled	1
	Moderately soiled	5
	Saturated	20
Clots	Small (size of a rupee coin smaller)	1
	Large (larger than a rupee coin)	5

Table II. Outcome Measurements

Parameters	Pre-treatment	Post-treatment	Remarks
Median PBAC score	272.0 (Range 123-865)	107.8 (Range 60.7 to 415)	t =20.20 p<0.001
Mean hemoglobin level (gm/dl)	9.42 (Range 7.85 to 11.42)	10.73 (Range 9.2 to 12.57)	t=25.7 P<0.001
Mean endometrial thickness (mm)	11.4 mm (Range 8 to 17 mm)	7.8 mm (Range 3 to 11 mm)	t=21.10 P <0.005
Presence of Clots (Proportion of subjects)	63/85	11/85	z=8.02 p<0.001
Dysmenorrhea (Proportion of subjects)	23/85	5/85	z=3.68 ; p<0.005

Table III. Subjective Assessment Of Amount Of Flow

Amount of flow	Nil	Light	Average	Heavy	Very heavy
Pretreatment	0	0	22	50	13
Posttreatment	15[a]	17	42	10	1

[a] Amenorrhoea was mostly noted in older (≥41 years) age group (13/39) rather than in younger age group (2/46).

Discussion

The use of ormeloxifene for menorrhagia is very limited even though it is likely to be a very effective treatment. An overview of phase III drug trials in India (Unpublished data given in Product Monograph – Torrent Pharmaceuticals Ltd.) proved its efficacy in the treatment of DUB. Their results correlate well with the present trial. Our improvement in heavy flow (85.7%) and dysmenorrhea (78.26%) in the present study is in concordance with that reported in phase III trial i.e., 87.78% and 80.85% respectively. Presence of clots is an obvious evidence of abnormally excessive flow as reported by Higham et al[6]. In the present study 85.71% (54/63)of patients reported improvement by absence of clots at the end of the therapy.

The number of napkins used was expected to be another criteria of improvement, though in research studies the gold standard for measuring blood loss remains the alkaline hematin test[7] . We opted to use the pictorial blood loss assessment chart (PBAC) used by Higham et al[6], a simple and less time consuming procedure which does not require the collection of sanitary products and avoids the costly chemical assay. PBAC scores and MBL are also well correlated (r=0.847)[6]. There was significant increase in hemoglobin concentration (1.31 g/dl average) after treatment.

Ormeloxifene has got an excellent safety profile and has been found to have very few side effects, limited to mild gastrointestinal symptoms (2.1%), weight gain (1.16%) and giddiness (1.17%). Amenorrhoea was noted in 15 subjects (17.64%), majority of them being peri-menopausal women and this was welcomed by them. It has been estimated that two million women in the United States present annually with complaints of excessive uterine bleeding and that about 150,000 undergo hysterectomy, which accounts for 20-30% of all hysterectomies performed[8]. Only 8.2% women (7 out of 85) in this trial had to undergo hysterectomy.

The cut-off value of less than 5mm to diagnose atrophic endometrium by TVS was taken as per criteria of Shia Salen[9].

Limitations of the present study include the absence of double blind placebo controlled method to eliminate information bias. Randomized controlled trials with larger subjects are needed to compare the drug to other medical therapies such as combined oral contraceptive pills, levonorgestrel releasing intrauterine systems, oral progestogens, anti-fibrinolytics and nonsteroidal anti-inflammatory agents (NSAIDs). Apart from its efficacy, ormeloxifene has shown its superiority by good compliance because of convenient dose schedule (once or twice a week) and cost-benefit for total therapy. Besides it does not increase the risk of breast cancer because of its anti-estrogenic action on the breast tissue.

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References

1. Hallberg L, Hodgahl AM, Nilsson L et al. Menstrual blood loss – a population study. *Acta Obstet Gynecol Scand 1966; 45: 320-51.*
2. Cole SK, Billewicz WZ, Thomsom AM. Sources of variation in menstrual blood loss – a population study. *J obstet Gynecol Br Commwlth 1971;78: 933 9.*
3. Gath D, Osborn M, Bungay G et al. Psychiatric disorder and gynaecological symptoms in middle aged women: a community survey. *BMJ. 1987; 294: 213-18.*
4. Coulter A, Kelland J, Peto V et al. Treating menorrhagia in primary care. An overview of drug trials and a survey of prescribing practice. *Int J Tech Assess Health Care 1995; 11 : 456-71.*
5. Winsor SHM, Fisher S, Hahn PM et al. Retrospective evaluation of the long term outcomes following conservative management of menorrhagia in ovulatory women. *J Soc Obstet Gynecol Can 1999; 2:155–63*
6. Higham JM, O'Brien PMS, Shaw RW. Assessment of menstrual blood loss using a pictorial chart. *Br J Obstet Gynaecol 1990; 97 : 734 9*
7. Hallberg L, Nillsson L. Determination of menstrual blood loss. *Scand J Clin Lab Invest 1964; 16: 244–8.*
8. Butler WJ. Normal and abnormal uterine bleding. In : Rock JA. Thompson JD eds. Te Linde's operative Gynecology. 8th ed. *New York. Lippincott Raven. 1997: 453-75.*
9. Shia Salen .The uterus and adnexa, In: Rumack CM; Wilson SR, Charboneau JW- Diagnostic Ultrasound-2nd edition. Vol 1- *New York. Mosby. 1998: 519-73.*