ORMELOXIFENE; MEDICAL MANAGEMENT OF DYSFUNCTIONAL UTERINE BLEEDING

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Abstract: To evaluate the efficacy of Ormeloxifene in DUB. Medical management of DUB is a challenging task and many drugs are available for this condition but show lack of consensus for medical treatment. Ormeloxifene mediates its effects by high affinity interaction with ER, antagonizing the effect of estrogen on uterine and breast tissue and agonizing the effect on vagina, bone, cardiovascular system. So it is suitable for medical management of DUB. Sixty five women aged between 30 to 50 were recruited for the study whom chief complaint was heavy menstrual flow. Ormeloxifene 60 mg was given orally twice in a week for first 12 weeks followed by once in a week for next 12 weeks. Menstrual blood loss measurements using subjective assessment of amount of flow, blood hemoglobin 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. The difference in mean heamoglobin concentration of 1.31gm/dl between pretreatment and post-treatment levels was also statistically significant (P<0.001). 87.05% showed a reduction in endometrial thickness as assessed by transvaginal sonography. 8.2% women needed hysterectomy. Ormeloxifene is an effective drug therapy in medical management of DUB.

Key words: Ormeloxifene, Menorrhagia

INTRODUCTION

Menorrhagia is define as excessive menstrual blood loss i.e more than 80ml per cycle. It affects approx15-30% of women at some stage In their reproductive lives [1-3]. After excluding all organic causes menorrhagia is termed as Dysfunctional uterine bleeding. Hystrectomy is still the only suitable treatment for those who have no further wish to concive [4]. Medical management DUB is a challenging task and many drugs are available for this condition but show lack of consensus for medical treatment [5]. Selective estrogen receptor modulators (SERM) are new category of therapeutic agents that selectively bind with
high affinity to estrogen receptors (ER) and mimic the action on some tissues and antagonize on other tissues.

Ormeloxifene one of the SERMs, is a chroman derivative, which has both estrogen agonist and antagonist in a ratio of 1:4. It is a nonsteroidal, nonhormonal pharmacologically inert agent which is metabolically and biologically safe and oncologically protective for both breast and endometrium. Antiestrogenic effects of ormeloxifene varies with the concentration gradient of the drug. At a lower dose of 30 to 60mg/week it completely blocks the mitosis in the uterine epithelial tissue. This prevents proper endometrial decidualization and thus effecting implantation failure and contraception. Dose of 120mg/week is effective in endometrial suppression and hemostasis, thus a suited remedy for menorrhagia. It exerts antiproliferative effect on endometrium hence used as a quick and effective endometrial hemostat for abnormal uterine bleeding.

Being SERM ormeloxifene is one that has no uterine stimulation, prevents bone loss, has no risk of breast cancer, active effect on lipids and cardiovascular system and maintains cognitive function of the brain. In summary it has antiestrogenic effects on the endometrium and breast but estrogenic effects on vagina, bone, CVS and CNS. Ormeloxifene can start anytime in the cycle, can be given to any age group, dose not suppress ovulation and can be stopped at any time.

There has been a 70-80% reduction in the number of hysterectomies performed for DUB. Preservation of uterus also helps safeguard ovarian function to the natural age of menopause. Medical management and avoidance of surgery is always recommended, because a short period of drug therapy successfully bridges the temporary phase of menstrual alterations, and young subjects settle down with normal cycles whereas elderly subjects attain menopause. The purpose of this study is to evaluate the efficacy of ormeloxifene in women with DUB.

**Materials and Methods**

The research project approved by the ethical committee, studied the effect of ormeloxifene on heavy menstrual blood flow. Subjects were recruited at random from outpatient department of Obstetrics and Gynecology, between July 2011 to June 2012. Women aged 30 to 50 years with the diagnosis of DUB, with cycle length of 20 to 40 days were selected for the study. Informed written consent was obtained. Exclusion criteria were: any pelvic pathology like fibroids, any ovarian pathology like polycystic ovarian disease, any cervical pathology like cervical hyperplasia, chronic cervicitis, any systemic disease like platelet disorder, coagulopathy, previous history of thrombosis, clinical evidence of jaundice. The main outcome measures were menstrual blood loss, blood haemoglobin levels and endometrial thickness in proliferative phase as studied by transvaginal sonography.

Assessment of menstrual blood flow was subjective and categorized as scanty, average and heavy blood flow, hemoglobin and endometrial thickness by TVS were measured initially and at the end of study.

**Results**

Sixty five women recruited in the study had subjective evidence of menorrhagia. Table 1 shows the different outcome measurements. The pretreatment baseline was heavy menstrual blood flow and post-treatment was average or scanty blood flow though 2 patients developed amenorrhea.

The mean pretreatment Hb concentration was 9.42g/dl with a range of 7.85 to 11.42g/dl. The mean post treatment Hb concentration was 10.73g/dl with a range of 9.2 to 12.57g/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 2.

Fifty four out of sixty five patients (87.05%) showed reduction in endometrial thickness as
measured by TVS in the proliferative phase. Two patients (3.08%) who developed amenorrhea had atrophic endometrium (less than 4 mm thickness).

The eleven women who continued to heavy blood flow were subjected to dilatation and curettage followed by histopathological study. Five women showed atypical endometrial hyperplasia were subjected to total hysterectomy, the incidence of hysterectomy being 8.2% (5/65) in the series.

**DISCUSSION**

The use of ormeloxifene for menorrhagia is very effective treatment. In our study improvement in heavy flow (87.05%) is very much concordance as reported by Higham et al. [6]. There is significant increase in hemoglobin concentration (1.31g/dl) after treatment. Ammenorrhea developed in two patients both of them being peri menopausal so this was welcomed by them. Only five women i.e 8.2% had to undergo hysterectomy in contrast to 20 to 30% of all hysterectomies performed in USA annually with complaints of menorrhagia [7].

Ormeloxifene has antiestrogenic and antiproliferative effect on endometrium. The drug reaches the serum concentration in 30 minutes and a peak in 4 hours hence it is quick acting. So used as a quick and effective endometrial hemostat for DUB. It has a prolonged half life of seven days. So compliance is very good i.e once or twice in a week. Recommended dose is 60 mg twice a week for three months and then reduced to once in week for next three months. The antiestrogenic property of ormeloxifene at endometrium has led to the selection of this agent as an endometrial hemostat in menorrhagia. Of particular note was the ability of these antiestrogenic to display substantial agonist activities in certain tissues like heart and bone. This selective estrogenic agonistic action makes ormeloxifene a preferred agent for treatment of menorrhagia of elderly subjects particularly.

Ormeloxifene is nonsteroidal, nonhormonal, pharmacologically inert, endocrinologically noninterfering, metabolically noncontroversial, biologically safe, oncologically protective i.e., both breast and endometrium remain protected. It is also devoid of androgenic ill effects such as acne and hirsutism.

Ormeloxifene in DUB can start anytime i.e during the bleeding episode or interval period. It is effective and quick acting so usually bleeding is controlled within 48 hours. It controls DUB of all ages and biologically safe for all ages. It offers perimenopausal bone and cardiovascular protection.

Medical management of DUB by ormeloxifene causes a 70-80% reduction in the number of hysterectomies performed for DUB [8]. Preservation of uterus also helps safeguard ovarian function to the natural age of menopause. Medical management and avoidance of surgery is always recommended because a short period

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**Table 1: Outcome measurements**

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>Parameters</th>
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</thead>
<tbody>
<tr>
<td>Mean Hb Level</td>
<td>9.42±1.42 gm/dl</td>
<td>10.73±2.57 gm/dl</td>
<td>t = 25.7 p &lt; 0.001</td>
</tr>
<tr>
<td>Thickness (mm)</td>
<td>Range (8-17) mm</td>
<td>Range (7.8mm-11) mm</td>
<td>t = 21.10 p &lt; 0.005</td>
</tr>
</tbody>
</table>

**Table 2: Subjective Assessment of amount of blood flow**

<table>
<thead>
<tr>
<th>Amount of Flow</th>
<th>Nil</th>
<th>light</th>
<th>Average</th>
<th>Heavy</th>
<th>Very Heavy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Treatment</td>
<td>0</td>
<td>0</td>
<td>22</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>Post-Treatment</td>
<td>15</td>
<td>17</td>
<td>42</td>
<td>10</td>
<td>1</td>
</tr>
</tbody>
</table>
of drug therapy successfully bridges the temporary phase of menstrual alteration and young subjects settle down with normal cycles whereas elderly subjects attain menopause.

CONCLUSION

Ormeloxifene has estrogenic and antiestrogenic effect. Its dose is convenient it is the oral drug devoid of any side effect can be taken by any age group, offers peri menopausal bone and cardiovascular, oncological protective to the breast and endometrium hence a good pharmacological agent in medical treatment of dysfunctional uterine bleeding.

REFERENCES