IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 13, Issue 6 Ver. V (Jun. 2014), PP 39-42
www.iosrjournals.org

Efficacy and Safety of Ormeloxifene in the Management of Dysfunction Uterine Bleeding

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Abstract:
Background: *Dysfunctional uterine bleeding (DUB) is the most common cause of abnormal vaginal bleeding during a woman's reproductive years. Regarding medical management of DUB, there is a general lack of evidence based approach, marked variation in the practice and continuing uncertainty regarding the most appropriate therapy. Ormeloxifine, a selective estrogen receptor modulator, is emerging as a safe and effective agent for dysfunctional uterine bleeding.*
Objective: *To evaluate the efficacy and safety of ormeloxifene in medical management of dysfunctional uterine bleeding.*
Study Design: *This was a prospective study conducted on DUB patients attending outpatient clinic in a tertiary care hospital.*
Materials and Methods: *50 patients, on whom diagnosis of dysfunctional uterine bleeding was made, were recruited for study. Patients were given ormeloxifine 60mg twice a week for 12 weeks and then once a week for 12 weeks. The primary outcome measures were menstrual blood loss (assessed by pictorial blood assessment chart score), hemoglobin concentration and endometrial thickness. The secondary outcome measures were acceptability and side effects of ormiloxifene.*
Results: *There was a significant reduction in median PBAC score from 322 to 54 after six months of treatment. The mean hemoglobin concentration increased significantly from 8.1 to 9.4 gms/dl with a rise of 1.3gm/dl ($p < 0.05$). The mean pretreatment endometrial thickness was 11mm and it decreased significantly to 8.4mm after 6 months of treatment with ormeloxifene ($p < 0.05$). 76% of the women showed marked subjective improvement in symptoms. The most common side effect reported was amenorrhoea (16%).*
Conclusion: *Ormeloxifene can be considered as an effective and safe therapeutic option for the medical management of dysfunctional uterine bleeding.*
Key words: *Dysfunctional uterine bleeding, SERM, ormiloxifene.*

I. Introduction

Dysfunctional uterine bleeding (DUB) is defined as abnormal, irregular, uterine bleeding in the absence of any systemic cause or organic disease of genital tract and is diagnosis of exclusion. It is the most common cause of abnormal vaginal bleeding during a woman's reproductive years.[1]

Altered hypothalamic pituitory ovarian function and or local changes in prostaglandin production can give rise to DUB. It is typically characterized by heavy, prolonged flow, with or without breakthrough bleeding. It occurs more frequently in anovulatory cycles than ovulatory cycles.[2] DUB is a common debilitating problem among women in all age groups and accounts for 20% of gynaecology office visit[3]. The most common drugs used for initial medical management of DUB include high dose estrogen, estrogen and progesterone,progesterone alone, antifibrinolytics, non-steroidal anti inflammatory drugs.Cyclical combined oral contraceptive pills were widely used previously but side effects have limited their use. Danazol, gonadotrophin releasing harmone analogues are all effective in terms of reducing menstrual blood loss but adverse side effects and cost limit their long term use.[4] Inspite of advances in minimal invasive surgical techniques, the best treatment for DUB is conventional hysterectomy for those who have completed their families.

Selective estrogen receptor modulators (SERM) selectively bind with high affinity to estrogen receptors and acts as estrogen agonist in some tissues and estrogen antagonists in others. Ormiloxifene, a third generation SERM, antagonises the effect of estrogen on uterine and breast tissue and stimulates its effect on vagina, bone, cardiovascular and central nervous system[5]. The effects of this SERM on the vascular

endometrium leads to decrease in blood loss and thereby amelioration of symptoms in dysfunctional uterine bleeding (DUB)[6]. Thus, it is especially beneficial in perimenopausal women as it has no uterine stimulation, prevents bone loss, does not increase the risk of breast cancer, lowers cholesterol level and maintains cognitive function of the brain. With this background, the present study was undertaken to study the efficacy of ormeloxifene in the treatment of DUB.

II. Aims & Objectives

TO evaluate the efficacy and safety of ormeloxifene in dysfunctional uterine bleeding.

III. Materials & Method

This prospective study was conducted in Lalla Ded hospital ,Government Medical College, Srinagar on patients attending out patients clinic. 50 women presenting with abnormal uterine bleeding without any organic, systemic or iatrogenic cause, were recruited for study. A detailed history was taken and complete examination was done. The investigation which were carried out included complete blood count, coagulation profile, thyroid profile, blood sugar, liver function test, kidney function test, ultrasound of the abdomen and pelvis and endometrial thickness measurement.

Exclusion criteria were pelvic pathologies like uterine fibroid, endometriosis, malignancies of genital tract, medical disease like liver dysfunction, heart disease, coagulopathies, renal disease, pregnancy, IUCD or pill users, lactating women in the first 6 months of postnatal period, thyroid disorder, history of abortion within last 3 months and hypersensitivity to drug.

Informed consent was taken from all the patients selected for study. All patients were given tablet ormeloxifene 60mg twice a week and then once a week for next 12 weeks. Patients were asked to maintain menstrual calendar. Patients were called at monthly interval. At each visit, a detailed menstrual history was taken and physical examination was done. Menstrual blood loss was measured objectively by a pictorial blood loss assessment chart (PBAC) score as described by Higham et al. PBAC is a simple and less time consuming procedure for objective assessment of menstrual blood loss. A PBAC score > 100 indicate a menstrual blood loss > 80ml and is considered diagnostic for menorrhagia.

		PBAC Scoring
Pads	Lightly soiled	1
	moderately soiled	5
	Saturated	20
Cloths:		
	small (smaller than a rupee coin)	1
	Large(large than rupee coin)	5

Haemoglobin estimation and endometrial thickness was measured at start of therapy and after 6 months of treatment. Subjective improvement and any side effects experienced by patients were noted.

IV. Observations & Results

50 women with the diagnosis of DUB were recruited for the study . The mean age of patients was 37 years with a range of 18-50 years. The mean parity was 3 and the mean duration of symptoms was 10.5 months (6-24 months range).

Clinical profile of patients.

S.No	Clinical parameter	Mean (Range)
1	Age	37 years (18-50 years)
2	Parity	3 (1-6)
3	Duration of symptoms in months	10.5 months (6-24)

Menstrual blood loss was assessed by PBAC and calculated at beginning, then at 3 months and at 6 months of treatment. The median pretreatment PBAC score was 322 and reduced to 54 at six months ($P < 0.05$).

The mean hemoglobin of the patients at the start of treatment was 8.1g/dl. After six month, the mean HB was 9.4g/dl. There was a significant increase in mean HB concentration with a rise of 1.3g/dl after 6 months of therapy with ormeloxifene. ($P<0.05$)

The pre and post treatment endometrial thickness was 11mm and 8.4mm respectively with a significant decrease of 2.6mm after 6 months. ($P<0.05$)

Outcome measure of the study after 6 months

Parameter	Pre-treatment	Post- treatment	P value
Median PBAC	322	54	
Mean Hemoglobin level (gm/dl)	8.1	9.4	
Mean endometrial thickness	11mm	8.4mm	

All patients were asked about the subjective improvement in their symptoms of DUB. 76% of patients (38 out of 50) showed marked improvement in symptoms. 4 patients had no improvement and 7 patients had mild improvement. Only 1 patient had an aggravation of symptoms during the therapy and hence the treatment was changed.

Subjective Assessment of Symptoms

Subject Improvement	Number	Percentage
No improvement	4	8
Mild improvement	7	14
Marked improvement	38	76
Aggravation of symptoms	1	2
Total	**50**	**100**

There was no major side effect with the therapy. The most common complaint was amenorrhoea which was seen in 8 patients (16%). Hypomenorrhoea was reported in 2 patients (4%). Gastric irritation, headache, abdominal pain were other symptoms reported but were not significant.

V. Discussion

Menorrhagia accounts for most of the referrals to gynaecological OPD and in majority of cases, no organ pathology is found. DUB is a diagnosis of exclusion. It occurs more commonly in the first 5 years after a woman starts menstruating and as she approaches menopause, but it can occur at any age.

The traditional surgical treatment for menorrhagia is hysterectomy. While it 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 mortality[8,9]. Endometrial ablation techniques offer an alternative surgical treatment option with significantly reduced postoperative morbidity[10]. They may be unsuitable for women wishing to retain their menstrual or reproductive functions and require technical expertise.

For women with DUB, who wish to retain fertility, pharmacological approaches are the only current available options. Antifibrinolytics, non-steroidal anti-inflammatory drugs, progesterones, combined estrogen and progesterone, danazol, GnRH analogues and levonorgestrel releasing intra uterine devices have all been used with varying results. The most commonly used drugs, however, are the progesterone norethisterone. Recent studies doubt its effectiveness in reducing menstrual blood loss[11]. Danazol, GnRH analogues are highly effective but their side effects make them suitable only for a short term use.

The ideal therapy should be a designer drug which can block the action of estrogen on the endometrium but not its beneficial effects on other tissue[1]. Selective estrogen receptor modulators are drugs that act in specific ways at each of the estrogen receptor site in different tissues[12]. Ormiloxifene is an optimally designed SERM with varied tissue response. It is indicated for the treatment of dysfunctional uterine bleeding at any age. It offers the additional advantage of relief of premenstrual syndrome in peri-menopausal women. However, it is not suitable for women desiring pregnancy in view of its contraceptive property.

The present study was conducted to evaluate the efficacy and safety of ormeloxifene in the management of DUB. The study showed that there was a significant reduction in menstrual blood loss with ormeloxifene, as assessed by fall in PBAC score and improvement in patients subjective symptoms. The median PBAC score decreased from 322 to 54 after 6 months of treatment and this fall in PBAC score was significant ($p < 0.05$). Kriplani et al[13] conducted a pilot study in which the median PBAC score was significantly reduced from 338 to 80 at 2 months and to 5 at 4 months with a 99.7% reduction in mean blood loss.

The results of our study suggests that there was a significant rise in haemoglobin concentration from 8.1 to 9.4g/dl after six months of treatment with a rise of 1.3g/dl. The endometrial thickness decreased from 11mm to 8.4mm with 6 months therapy of ormeloxifene and this decrease was found to be statistically significant. Similar to present study, Dhananjay et al[14] found a statistically significant increase in hemoglobin concentration (8.26 to 10.59g/dl, $P<0.001$) and a statistically significant decrease in endometrial thickness (9.83 to 4.89; $P<0.001$) after 3 months of treatment with ormeloxifene. Dadich et al[1] also found a significant reduction in median PBAC score (379 to 15), number of days of menstruation and number of sanitary napkins used after 6 months of ormeloxifene therapy. Biswas et al [5] found that the difference between pre-treatment and post-treatment median PBAC score of 97.2 and the rise in mean haemoglobin concentration of 1.3g/dl was statistically significant ($P<0.001$)

The present study showed a significant improvement of patient's condition both subjectively and objectively. 76% of patients showed marked improvement of symptoms. In a study done by S. Dadich et al, [1] 92% patients had complete relief from excessive blood loss. N. Agarwal et al[4] had conducted a study in which 88.33% of patients had marked improvement of symptoms.

Ormeloxifene was very well tolerated and practically there was no undesirable side effects. Amenorrhoea was the most common side effect seen in 8 patients (16%). Amenorrhoea was a common symptoms seen in different studie with a wide range of 8% to 42.9%[1,4,6].

VI. Conclusion

DUB is a very common disorder at all ages from menarche to menopause. Our study concluded that ormeloxifene is suitable for the treatment of DUB in all age groups with effective therapeutic safety and with least side effects. Our study also showed that the compliance of the patients is good because of convenient dosage schedule. Thus, ormeloxifene can be considered as an effective and safe therapeutic option for the medical management of dysfunctional uterine bleeding. However, further studies with large sample size are needed to throw light regarding the efficiency and safety of the agent.

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