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Original Research Article

Efficacy and safety of ormeloxifene in the management of dysfunctional uterine bleeding

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ABSTRACT

Background: The term dysfunctional uterine bleeding (DUB) is used for abnormal uterine bleeding occurring in the absence of identifiable pathology. A number of drugs are available for management of DUB- nonsteroidal anti-inflammatory drugs, tranexamic acid, ethamsylate, hormones like Oral contraceptives progestins etc. The present study was done to determine the efficacy and safety of ormeloxifene in the management of DUB.
Methods: This prospective clinical study involved 50 cases with DUB who were treated with ormeloxifene 60 mg tablet twice a week for first 12 weeks and the once a week for next 12 weeks. They were followed after 6 months of therapy. The outcome was studied by assessment of menstrual blood loss by PBAC score, Hb level in g/dl, endometrial thickness in mm, relief of dysmenorrheal and any side effects of drugs.
Results: The median PBAC score was significantly reduced from 316 to 52 after 6 months of therapy. The mean Hb concentration was significantly increased from 7.8 g/dl to 9.1 g/dl at 6 months of therapy. The mean endometrial thickness was reduced from 10 mm to 7.9 mm after 6 months of therapy. 66% of women showed marked subjective improvement in symptoms. Amenorrhea was the main side effect (12%).
Conclusions: Ormeloxifene has significant effect in reducing endometrial thickness, decreasing the amount of menstrual blood loss, reducing dysmenorrhea and thereby improving the general condition of the patient. It is definitely a better alternative to hysterectomy in women who wish to avoid surgeries and maintain their reproductive functions.

Keywords: Dysfunctional uterine bleeding, Ormeloxifene, SERM

INTRODUCTION

Abnormal uterine bleeding (AUB) is a symptom and not a disease.AUB is an overarching term used to describe any departure from normal menstrual cycle pattern. The key characteristics are regularity, frequency, heaviness and duration of flow but each of these may exhibit considerable variability.[1] When causes are demonstrable, they are grouped as organic, but when causes are not obvious, they are labelled as dysfunctional uterine bleeding (DUB). DUB is essentially a diagnosis of exclusio.[2] DUB is often classified into ovulatory and nonovulatory. Ovulatory DUB can present either as polymenorrhea and polymenorrhagia or simply heavy or prolonged menses at normal intervals. Ovulatory DUB is due to corpus luteum defects either irregular ripening or irregular shedding of the endometrium or due to abnormal stimulation of hypothalamic-pituitary axis which occurs in conditions like post-pregnancy where pituitary function is disturbed or day to day stress elevating factors.[3] Anovulatory bleeding results from estrogen withdrawal reflecting the transient fall in

estrogen level accompanying regression of follicular cohort or from estrogen breakthrough due to focal breakdown of an overgrown and structurally fragile endometrium under continuous estrogen stimulation.[4] AUB can cause haemorrhagic shock, anemia, iron deficiency and decrease quality of life.[5] It affects 10-30% of women at some stage in their life.[6,7] There is no definite pathology at hysterectomy in approximately 50% of cases.[8]

The treatment of DUB is demanding task and requires identification of responsible mechanism whether ovulatory or nonovulatory. The medical options for initial management of DUB include antifibrinolytics, combined estrogen and progesterone or progesterone alone, high dose estrogen, gonadotropin releasing hormone analogues, antigonadotropins NSAID's, copper and levonorgestrol containing IUCD and endometrial ablation/resection are to be known. However, still hysterectomy is only available therapy. Ormiloxifene is one of the selective estrogen receptor modulator (SERM) which binds with estrogen receptors and mimics the effect of estrogen in some tissues.[9] It is non-steroidal, non –hormonal oral contraceptive developed by central drug research institute, Lucknow.[10] However, Ormeloxifene acts as estrogen antagonist in uterus (endometrium), breast tissues which lead to endometrial atrophy and the decreased menstrual loss and have stimulating effect on vagina, bones, cardiovascular system and central nervous system.[11] In this era of organ preservation ormeloxifene can serve as good alternative to hysterectomy. Therefore, the aim of present study was to evaluate the effect of ormeloxifene drug in women with dysfunction uterine bleeding. And to evaluate efficacy and safety of ormeloxifene in DUB.

METHODS

The prospective study was carried out in SKIMS hospital, Srinagar on patients attending outpatient clinic. 50 cases were enrolled in the study with DUB. A detailed history was taken and examination done. The investigations which were carried out included complete blood count, coagulogram, thyroid profile and ultrasound of abdomen and pelvis with endometrial thickness measurement.

The exclusion criteria were pelvic pathologies like uterine fibroid, adenomyosis, genital malignancies, medical diseases like liver dysfunction, heart disease, migraine, stroke, renal disease, hypo and hyperthyroidism, platelet disorders and coagulopathy, previous history of thrombosis, pregnancy, abortion, use of IUCD, or oral contraceptive, lactating women in first 6 months of post-natal period and hypersensitivity to drug. Informed consent was taken. All cases were given ormeloxifene 60 mg twice a week for 12 weeks and then once a week for next 12 weeks. Follow up was done at 6 months or earlier if needed. The primary outcome measures were menstrual blood loss, haemoglobin measurement and endometrial thickness in proliferative phase of menstrual cycle by TVS. The secondary measures were the acceptability and side effects of ormeloxifene.

Menstrual blood loss was objectively assessed by Pictorial blood loss assessment chart (PBAC).PBAC score ≥100 is equivalent to menstrual blood loss ≥ 80 mland is considered diagnostic of menorrhagia.[12]

PBAC score

- Pads highly soiled = 1
- Moderately soiled = 2
- Saturated = 20
- Clots
  - Small = 1
  - Large = 5

RESULTS

Fifty cases with DUB were recruited in the study; with PBAC score >100 in the pre-treatment cycle.

Table 1: Clinical profile of patients.

Clinical profile	Mean
Age	39 years (19-48)
Parity	3(1-6)
Duration of symptom	11.5 months (6-22)

Table 2: Outcome measure of study after 6 months.

	Pre-treatment	Post-treatment	P value
Median PBAC	316	52	< 0.05
Mean Hb level	7.8	9.1	<0.05
Mean endometrial thickness	10 mm	7.9 mm	<0.05
Presence of clots	33/50 (66%)	19/50 (38%)	<0.05
Dysmenorrhea	19/50 (38%)	6/50 (12%)	<0.05

The mean age of subjects was 39 years, mean parity 3 and mean duration of symptoms 11.5 months. Menstrual blood loss, haemoglobin level and endometrial thickness were observed before starting treatment and then after 6

months of treatment as shown in the table 2. The median PBAC score was 316 which was reduced to 52, the reduction was statistically significant (p<0.05). In the present study presence of clots reduced from 66% to 38% along with significant reduction in dysmenorrhea. Most of the women were anemic with mean Hb of 7.8 gm, it was significantly raised to 9.1 gm at 6 months of therapy. The mean endometrial thickness was 10 mm which reduced to 7.9 mm after treatment. The reduction was statistically significant.

Table 3: Subjective assessment of symptom.

Assessment of symptom	Number of cases (%)
No improvement	7 (14%)
Mild improvement	8 (16%)
Marked improvement	33 (66%)
Aggravation of symptom	2 (4%)

Marked improvement was seen in 66% of cases, no improvement in 14% of cases and aggravation of symptom in 4% of cases.

Table 4: Side effects with Ormeloxifene.

Side effects	Number of cases
Ammenorrhea	6 (12%)
Hypomenorrhea	3 (6%)
Gastric irritation	-
Headache	-
Pain	-

Most common side effect was amenorrhea (12%) followed by hypomenorrhea (6%).

DISCUSSION

DUB occurs more commonly in the first five years after menarche and during perimenopausal period, but it can occur during reproductive period. For women with DUB who wish to retain fertility, pharmacological approaches are the only currently available options. In our study we have analysed the efficacy of ormeloxifene in patients with DUB and our results suggested that there was significant reduction of menstrual blood loss.

The median PBAC score reduced from 316 to 52 with statistically significant difference (p<0.05) after 6 months of tre- atment (Table 2). Biswas SC et al, found that the median PBAC score was reduced from 272 to 107.8 at the end of 24 weeks of treatment.[13] Kriplani A et al, conducted a pilot study in which the median PBAC score was significantly reduced from 388 to 5 at 4 months with 98.7% reduction.[14] Bhattacharyya TK et al, in his study where 180 DUB cases in three groups were administered ormeloxifene, norethistrone and iron concluded a marked reduction in mean PBAC score from 108.70 to 62.48 in the ormeloxifene group but in norethistrone group it was reduced only to 94.07 from 113.87.[15]

The mean endometrial thickness at the beginning of study was 10 mm, which was reduced to 7.9 mm at the end of 6 months of treatment (p <0.05) (Table 2). Biswas SC et al, found reduction of endometrial thickness from 11.4 mm pre-treatment to 7.8 mm at the end of 6 months of therapy (p <0.001).[13] Kriplani A et al, documented in their study a marked reduction in endometrial thickness after 4 months of therapy.[14] In the study by Bhattacharyya TK et al, the pre and post treatment values differed significantly in all the three groups treated with ormeloxifene, norethistrone and iron respectively.[15]

In our study the mean haemoglobin level at the end of 6 months after treatment with ormeloxifene was 9.1 gm/ dl compared to the pre treatment level of 7.8 gm/dl. The increase in haemoglobin was statistically significant (p <0.05) (Table 2). Bhattacharyya TK et al, concluded increased Hb level all the three groups but maximum in patients who were given ormeloxifene followed by norethistrone and then iron.[15] In study by Aggarwal N, et al, the increase in mean haemoglobin level was more in ormeloxifene group than norethistrone group.[16]

Dysmenorrhea got reduced from 38% to 12% with statistically significant difference (p< 0.05) at the end of 6 months of therapy (Table 2). Similar results were seen in Kriplani A et al, study.[14] In this study, marked improvement was seen in 66% of patients, which was similar to Kriplani A et al, and Biswas SC et al, studies.[13,14]

Side effects gastric irritation and headache were not severe enough to interfere with the compliance (Table 4). Slightly more side effects were demonstrated in study by Kriplani A et al, gastric upset (7.1%), vague abdominal pain and headache (4.8%) cases.[14] Amenorrhea occurred in 12% and hypomenorrhea in 6% of patients at the end of 6 months of therapy.

No case of ovarian enlargement was seen in our study whereas Kriplani A et al, found 7.1% cases with ovarian enlargement after treatment with ormeloxifene.[14] Biswas SC et al, concluded that ormeloxifene has very few side effects, limited to mild gastrointestinal symptoms (2.1%), weight gain (1.16%) and giddiness (1.17%).[13]

CONCLUSION

Ormeloxifene has significant effect in reducing endometrial thickness, decreasing the amount of menstrual blood loss, reducing dysmenorrhea and thereby improving the general condition of the patient. It is definitely a better alternative to hysterectomy in women who wish to avoid surgeries and maintain their reproductive functions. It has convenient dose schedule of once or twice a week and is cost effective. It can be used in any age group and is oncologically protective to breast and endometrium. It is well tolerated and a safe alternative for medical management of DUB.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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