Dysfunctional uterine bleeding: ormeloxifene versus combined oral contraceptive pills

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ABSTRACT

Background: Dysfunctional uterine bleeding is abnormal bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy. Globally, health care systems are focusing on low morbidity and low cost therapeutic interventions. Hence, medical treatment for DUB is high on the priority list. This comparative study was conducted to analyse the efficacy of ormeloxifene and combined oral contraceptive pills in reducing the blood loss and endometrial thickness in cases of DUB.

Methods: This prospective study was conducted on women with dysfunctional uterine bleeding, who attended Gynaecology OPD at Hind Institute of Medical Sciences, between August 2015 and April 2016. After applying inclusion and exclusion criteria, 72 women diagnosed with DUB were enrolled randomly in two groups A and B. Group A was treated by Ormeloxifene and Group B patients were treated with combined oral contraceptive pills for three consecutive cycles. The efficacies of the studied drugs were compared by analyzing the mean change in the pre and post treatment PBAC score, haemoglobin level and endometrial thickness using unpaired t-test.

Results: Orlmeloixifene was found to be significantly more effective (p <0.0001) than OCPs in controlling the menstrual blood loss (79% reduction in group A Vs 55.5% reduction in group B). Reduction in endometrial thickness was also more in the group receiving Orlmeloixifene, however this was statistically not significant (p = 0.19). No major side effect observed with the use of Orlmeloixifene.

Conclusions: Ormeloxifene can be an effective and safe therapy in the treatment of Dysfunctional uterine bleeding.

Keywords: Dysfunctional uterine bleeding, Oral contraceptive pills, Ormeloxifene, Selective estrogen receptor modulator

INTRODUCTION

Abnormal uterine bleeding is a significant health care problem for women, their families, and society as a whole. Up to 30% of women will seek medical assistance for this problem during their reproductive years. Because most cases are associated with anovulatory menstrual cycles, adolescents and perimenopausal women are particularly vulnerable. In today’s world, where women represent a major sector of paid force in both the developing and developed countries, any regular source of debility like DUB has adverse economic, social and personal consequences.

Dysfunctional uterine bleeding is abnormal bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy. It reflects a disruption in the normal cyclic pattern of hormonal stimulation to the endometrial lining which is thought to be caused by dysfunction of hypothalamic-pituitary-ovarian axis. DUB is a frequent indication for hysterectomy in developing countries. Globally, health
care systems are focusing on low morbidity and low cost
therapeutic interventions. Hence, medical treatment for
DUB is high on the priority list.

Medical management of DUB is a challenging task. The
options for initial management of DUB include antifibrinolytics, nonsteroidal anti-inflammatory drugs
(NSAIDs), combined estrogen and progesterone pills,
progesterones alone, high dose estrogens, gonadotropin-
releasing hormone agonists, danazol and levonorgestrel
releasing intrauterine systems. Cyclical combined oral
contraceptive pills are widely used but side effects,
especially in women over 40 years of age, have restricted
their use. Danazol, progesterone and gonadotropin-
releasing hormone analogues are all effective in terms of
reducing menstrual blood loss, but adverse effects and
costs limit their long-term use.

For the treatment of DUB authors need a drug, which
blocks the action of estrogen on endometrium(anti-
estrogenic) but not its beneficial actions on other tissues.
Selective estrogen receptor modulators (SERMs) have been identified to occupy a place in between estrogens
and antiestrogens.

These compounds have estrogenic activities, which are
tissue selective. Ormeloxifene is an optimally designed
SERM, which behaves like an estrogen antagonist in
uterus with mild estrogenic action on vagina, bone and
serum lipids.6,8 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. It has the additional advantage of
reducing premenstrual symptoms, dysmenorrhoea and
mastalgia.9

When ormeloxifene was used as a contraceptive, its
beneficial effects on menorrhagia and endometriosis were
observed, which led to controlled trials for the
management of menorrhagia after approval was given by
the Indian Drug Regulatory Authorities for this
indication.

METHODS

A prospective study was conducted on women who were
diagnosed as a case of dysfunctional uterine bleeding at
out-patient department of Obstetrics and Gynaecology at
Hind Institute of Medical Sciences, Safedabad, Barabanki
between August 2015 and April 2016.

Out of total of 345 cases of abnormal uterine bleeding,
115 were found to have DUB. Total 72 patients were
selected according to exclusion and inclusion criteria.
Written informed consent for drug trial was taken.

Inclusion criteria

• Women between menarche and menopause
• AUB cases having no evidence of pelvic pathology
  on clinical examination or USG.

Exclusion criteria

• Pregnancy related bleeding like abortion or ectopic
  pregnancy
• Hypersensitivity to the drug
• Any hormonal therapy including oral contraceptive
  pill usage within last 3 months
• Any IUCD used or removed within last 6 months.
• Positive cervical cytology and colposcopic
  examination or suspicious cervix
• History of breast malignancy or any palpable lump in
  breasts
• Current genital infection
• Active bleeding necessitating emergency treatment
• Patient with severe anaemia (Hb <6 gm %)
• Any systemic diseases such as liver disorders,
  platelet disorder or coagulopathy
• Previous history of thrombosis or of migraine.

Selected patients of dysfunctional uterine bleeding who
consented for drug trial study and for regular follow up,
were included in the study and were divided into
following two groups:

Group A (Ormeloxifene group):

It was comprised of 36 patients who were prescribed
Ormeloxifene 60 mg twice a week for twelve weeks.

Group B (Combined oral contraceptive group):

This group was comprised of 36 patients who were
prescribed combined oral contraceptive pills (containing
ethinyl estradiol 30 μg and levonorgestrel 0.3 mg) for
twenty-one days starting from third day of menses
followed by seven pill free days. This treatment was
continued for three consecutive cycles.

All women were instructed to use sanitary napkin of
similar kind, not containing absorbent gel. A detailed
menstrual history and physical examination was done at
each visit at monthly interval. Any side effects observed
were noted. The subjective improvement of symptoms
and acceptability of drugs were enquired. The efficacy of
drugs, subjective and objective findings of improvement
in the condition of patient, tolerance to the drug and side
effects were noted.

The main outcome to be measured were menstrual blood
loss by PBAC score, blood hemoglobin levels in gm/dl
and endometrial thickness in mm, on 18-21 day of
menstrual cycle by trans-vaginal sonography (TVS).

Pictorial Blood loss Assessment Chart (PBAC) (Higham
et al., 1990) 10 was used to measure the menstrual blood
loss (MBL). Scores were assigned to different degrees of
soiling of sanitary napkins and number and size of clots passed at every cycle as per Figure 1.

| Pads                | 1 point       | For each lightly stained pad
| 5 points           | For each moderately stained pad
| 20 points          | For each completely saturated pad
| Tampons            | 1 point       | For each lightly stained tampon
| 5 points           | For each moderately stained tampon
| 10 points          | For each completely saturated tampon
| Clots              | 1 point       | For each small clot (size of a rupee coin/smaller)
| 5 point            | For each larger clot (larger than a rupee coin)

**Figure 1: Blood loss assessment chart.**

**Statistical analysis**

PBAC score, haemoglobin concentration and endometrial thickness were measured before the start of therapy and at end of 3 months i.e. after the completion of therapy. Statistical parameters were used as Mean±Standard Deviation and data were analysed using the paired t test. The change in mean PBAC and endometrial thickness in two groups were compared using unpaired t-test. Statistical significance was taken at p value ≤ 0.05.

**RESULTS**

![Figure 2: Group A (Ormeloxifene) Comparison between pre-treatment and post treatment Values.](image)

Out of these 72 patients of DUB 17 were lost to follow up and hence were excluded from the study. In Ormeloxifene group (group A, N=27), patients showed a significant reduction in mean PBAC score from 258.44 to 54.24 i.e. 79% reduction in menstrual blood loss. Similarly, a significant reduction in endometrial thickness was seen after treatment (P value<0.0001). A significant improvement in anemia was also seen inspite of no iron therapy given along with Ormeloxifene therapy (Figure 2).

In Combined oral contraceptive group (group B, N=28), p value <0.0001 indicates significant reduction in mean PBAC score from 221.34 to 98.45 (55.5%) after treatment. A significant reduction in endometrial thickness (P <0.0001) was also seen. A significant rise in haemoglobin level was observed (P<0.0001) after three months treatment with combined oral contraceptive pills, with no iron supplementation (Figure 3). On comparing group, A and group B, ormeloxifene was found significantly better than combined OCP in reduction of menstrual blood loss (79% vs 55.52% reduction with p value <0.0001) in cases of DUB. Reduction in mean endometrial thickness was also better in Ormeloxifene group than in combined OCPs group, but statistically it was not found significant (p value- 0.19).

![Figure 3: Pre-treatment and post-treatment values in Group B (Combined OCPs).](image)

There was no major side effect with Ormeloxifene. Amenorrhea was the main symptom seen in 5 cases (18.5%). Nausea, vomiting, ovarian cysts and headache were other side effects, but neither was significant enough to stop the therapy. In patients receiving combined oral contraceptive pills main symptom was gastric upset (in 32% of cases). Breast tenderness and weight gain were other symptoms.

**DISCUSSION**

The problem of dysfunctional uterine bleeding i.e. excessive or prolonged regular or irregular menstrual bleeding in the absence of overt uterine pathology,
endocrine or haematological disorder is a common reason for consultation in gynaecological out-patient departments. In recent years basic physiological research has resulted into a greater depth of insight into the mechanisms involved in the control of normal menstruation and the pathophysiology of dysfunctional uterine bleeding (DUB).

DUB can occur at any time between puberty to menopause and may be either ovulatory or anovulatory. A history of excessive bleeding with regular menstrual cycles is usually associated with ovulation. An anovulatory pattern of bleeding with erratic intervals between menstrual periods can also occur. Typically, the anovulatory pattern occurs at puberty prior to the onset of regular menstruation and also in women in their mid-30s onwards. It may also be seen in women with PCOD where there is peripheral conversion of androgens to estrogens. Ovulatory bleeding patterns are more common than anovulatory.

Newer drug therapies and the development of less invasive surgical techniques are in need of further clinical trials. The approach to management is to ensure general well-being and improve quality of life in addition to control the bleeding. Medical management and avoidance of surgery is always recommended, as the short period of drug therapy bridges the temporary phase of menstrual alterations successfully, wherein young subjects settle down with normal cycles and elderly subjects attain menopause. Ormeloxifene can be a good option with its properties of creating a hypoestrogenic environment without disturbing other estrogenic positive effects. Side effects like weight gain or breast tenderness, depression, mood changes, mastalgia and poor libido are not there with Ormeloxifene. It is also devoid of androgenic ill effects such as acne and hirsutism. Being a metabolically non-controversial agent, complications such as hypertension, coagulation disorders, hyperglycaemia and abnormal lipid profile, which are common with combined OCP, do not occur.

Ormeloxifene also offers perimenopausal bone and cardiovascular protection. It is found oncologically protective to the breast and the endometrium.

In present study authors have analyzed the efficacy of Ormeloxifene in patients with dysfunctional uterine bleeding and our results suggested that there was a significant reduction (p value <0.0001) in menstrual blood loss (mean PBAC score reduction of 79% from 258.44 to 54.24) after three months of treatment. These results are consistent with the study conducted at AIIMS by Kriplani A. et al, which showed reduction in median PBAC score from 388 (range 169-835) to 80 (range 0-730) and 5 (range 0-310) at 2 and 4 months respectively (p value <0.001).11 The reduction in PBAC score was 97.7% at 4 months. Shravage et al, 2011 concluded that there was a significant reduction in the menstrual blood loss of 85% in patients treated with Ormeloxifene.12

The results of the present study showed that there was a significant rise of haemoglobin of 1.6gm/dl (p <0.0001) after three months treatment with Ormeloxifene. It is consistent with other studies. Dhananjay BS et al, 2012 showed that there was a statistically significant increase in the haemoglobin level (p <0.001) after the treatment with ormeloxifene.13 Agarwal, et al also concluded that mean pretreatment Hb concentration significantly increased from 9.04gm% to 10.01 gm% at 3 months and to 10.86 gm% at 6 months (p <0.0001) in patients of DUB treated with Ormeloxifene.14

Shravage et al, found that the mean pre-treatment endometrial thickness was reduced from 7.81 mm to 4.94 mm after 3 months of therapy.12 Dhananjay BS et al, 2012 showed that there was a statistically significant reduction in the endometrial thickness (p< 0.001) after the treatment with ormeloxifene.15

In present study mean pre-treatment endometrial thickness reduced from 9.4mm to 5.8mm after treatment, showing a significant reduction (p<0.0001). A total of about 81% of patients responded well with Ormeloxifene. The results were corresponding to the results of above mentioned studies.

CONCLUSION

From above observations, it can be concluded that the ormeloxifene is more effective than combined oral contraceptive therapy in controlling the menstrual blood loss in cases of DUB. Apart from its efficacy, Ormeloxifene has shown its superiority by good compliance and less stringent eligibility criterion. Thus, it may be considered for the medical management of idiopathic menorrhagia, especially in peri-menopausal women, in adolescents and in women who wish to preserve their fertility.

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