



STUDY OF EFFICACY AND SAFETY OF DIENOGEST IN MANAGEMENT OF ABNORMAL UTERINE BLEEDING.

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ABSTRACT

Objective: To evaluate the efficacy and adverse reactions of Dienogest in patients with abnormal uterine bleeding. **Methods:** This was single centred, open label, 6 months prospective study. 52 patients with complaints of abnormal uterine bleeding having PBAC Score more than 100 were enrolled in study. Dienogest 2mg once a day was given for 3 months. At follow ups, patients were assessed for Endometrial thickness by USG, Haemoglobin level, PBAC score and adverse effects of drug therapy. **Results:** A total 52 patients with the mean age of 32.88 ± 6.97 were enrolled, in which 41 patients completed the follow up. There was statistically significant decrease in endometrial thickness, haemoglobin level and PBAC score. **Conclusion:** Thus Dienogest, an oral progestin is effective in medical treatment of abnormal uterine bleeding.

KEYWORDS: Abnormal uterine bleeding, PBAC score, Dienogest

INTRODUCTION

Abnormal uterine bleeding (AUB) is one of the most common conditions for which women consult their gynecologists. AUB may be defined as any variation from the normal menstrual cycle, including alteration in regularity, frequency of menses, duration of flow and amount of blood loss.^[1] Basically it is a symptom and not a disease. AUB can occur at any age in various forms and has different modes of presentation.^[2,3] Abnormal uterine bleeding during reproductive age can result from a broad spectrum of conditions ranging from physiological process to malignant lesions involving organic, systemic, and hormonal responses. It may be due to fibromyoma, adenomyosis, endometrial polyp, ovarian tumor, pelvic inflammatory disease (PID), endometrial hyperplasia, endometrial carcinoma, hormonal imbalance (like hypothyroidism), or hypothalamo pituitary ovarian axis disturbances.^[4,5,6] While in women of child bearing age pregnancy is the first consideration who present with abnormal uterine bleeding.^[7,8] Potential causes of pregnancy-related bleeding include spontaneous pregnancy loss (miscarriage), ectopic pregnancy, placenta previa, abruptio placentae, and trophoblastic disease.

About 9 to 16% of women experience episodes of abnormal uterine bleeding at sometimes during the reproductive years of life. Its common during extremes of reproductive life, following pregnancy and lactation.^[9] It is generally agreed that a normal bleeding episode comprises a menstrual blood loss volume in the range of

30–40 mL with an upper limit of 80mL.^[10,11] A menstrual cycle of fewer than 21 days or more than 35 days or a menstrual flow of fewer than two days or more than seven days is considered abnormal.

Common symptoms of abnormal menstruation include: bleeding that soaks through one or more sanitary pads or tampons every hour for several consecutive hours, bleeding so heavy one needs to double up on sanitary protection, bleeding that causes one to change protection during the night, a period lasting longer than seven days, menstrual flow containing large blood clots, heavy periods that interfere with one's regular lifestyle (i.e. physical activities, career, recreation, self-confidence, constant pain in one, s lower abdomen during one, s severe cramps or headaches during period tiredness, fatigue or shortness of breath (symptoms of anemia), depression or moodiness during one, s period A total of 18 epidemiologic studies were identified reporting a world wide prevalence rate of AUB of between 4 to 52%.(Fraser et al).^[9]

As AUB has a great burden on society. It is a major cause of morbidity in women. Women with AUB may experience pain, embarrassment, inconvenience, and ritualistic behavior to avoid social embarrassment that can have a significant impact on their lives.^[12] Not surprisingly, women with AUB report a significantly poorer quality of life when compared to unaffected women of similar ages. Moreover, up to \$12 billion is spent annually in the United States to treat AUB.^[13]

Medical as well as surgical treatments available for the patients to overcome this morbidity.

For reduction of menstrual bleeding in women with abnormal uterine bleeding presumed secondary to endometrial dysfunction, the levonorgestrel intrauterine system (71–95% reduction), combined OCPs (35–69% reduction), extended cycle oral progestins (87% reduction), tranexamic acid (26–54% reduction), and NSAIDs (10–52% reduction) were all effective treatments. So we can say hormonal and nonhormonal therapeutic options are available to patients.

In our study we had seen effects of Dienogest treatment in patients of abnormal uterine bleeding on endometrial thickness, haemoglobin, PBAC Score.

The new Dienogest pill recently received U.S. Food and Drug Administration (FDA) approval to treat heavy menstrual bleeding in women without diagnosed uterine conditions in 2012. Dienogest is the first non-alkylated 19-norprogesterin on the market. This so-called hybrid progestin combines the typical qualities of the modern 19-norprogesterins with those of natural progesterone and synthetic hydroxyprogesterone derivatives. Dienogest at 2mg/day induces anovulatory state with complete inhibition of ovulation. In large clinical trials of women with heavy menstrual bleeding, the dienogest pill decreased blood loss volume by a median of 81%.

MATERIALS AND METHODS

The study is conducted after approval from institutional ethical committee. It is interventional, nonblind study of duration of one year from November 2016 to October 2017.

Patients diagnosed case of abnormal uterine bleeding attending outpatient department Obstetrics and Gynaecology Swaroop Rani Nehru hospital, an associated tertiary care centre of Moti Lal Nehru Medical college Allahabad will be included in study.

Patients included women aged ≥ 18 to $45 <$ years with a newly diagnosed case of abnormal uterine bleeding, Must be able to understand and follow study related advice, Informed consent will be taken from the patient.

Patients were not included in study were not willing to give consent, AUB as a result of pregnancy and puerperal complications, Bleeding disorders, Females having haemoglobin < 6 gm/dl, medical disorders like liver dysfunction, heart disease, migraine, stroke, renal disease, hypo/hyperthyroidism.

Patients were diagnosed as AUB on the basis of history and clinical examination accompanied with routine and specific investigations blood group, Haemoglobin (gm/dl), Rh, TLC, DLC, VDRL, HBsAg, HIV-I & II, fasting & postprandial blood sugar, liver function test, renal function test and complete urine examination.

Baseline thyroid function test and urine pregnancy test were done to exclude thyroid disorder and pregnancy. Coagulation profile and bleeding time were done to exclude bleeding disorders. Pap smears were taken and endometrial biopsy was taken.

The Dienogest drug was administered orally for 3 months. Dose will be given 2mg/day.

The patient were asked to use certain sanitary napkins which had similar absorbent capacities and were advised to maintain a menstrual diary to record the total number of days of bleeding, number of sanitary pads used, Number of sanitary pads used each day (24 hour period) were counted. A score for each day was calculated and then score was added up at the end of the month.

Number and sizes of clots passed were also noted and also any episode of flooding. Degree of soaking of each pad, number and size of clots passed.

The follow up visits which were conducted at third and six months respectively. Patient were assessed for improvement of symptoms, compliance, regularities. Assessment was done in the form of amount of bleeding (which was assessed by PBAC score), recurrence of symptoms and also the side effects of each drug. Patient's endometrial thickness and haemoglobin were measured after 3 months and 6 months of the treatment.

Menstrual blood loss was measured objectively by pictorial blood loss assessment chart (PBAC) score as described by Higham et al. PBAC is a simple procedure for objective assessment of menstrual blood loss. The Pictorial Blood loss Assessment Chart (PBAC) Scoring was then accordingly to assess menstrual blood loss in each menstrual cycle. A PBAC score > 100 is considered diagnostic for menorrhagia (Higham JM et al 1990).^[14]

METHODS APPLIED FOR VARIOUS TEST

Endometrial Thickness- It was measured in department of radiology Swaroop Rani Nehru Hospital. Endometrial thickness was measured at first visit and then after 3 months and 6 months after treatment Dienogest.

Haemoglobin- Sample was given to institutional pathology lab of Swaroop Rani Nehru hospital. Reports were collected from pathology department.

PBAC Score- In this study, objective assessment of menstrual blood loss was done by Pictorial Blood Loss Assessment Chart (PBAC) as devised by Higham et al. PBAC is a simple and less time consuming procedure for objective assessment of menstrual blood loss.

PBAC Score is useful in evaluating menorrhagia in the clinic setting. It can be used as a tool to measure response of menorrhagia to different forms of treatment. Using the scales as described described below the total

score is calculated by adding up the sum of all scores for the sanitary napkins used in the menstrual cycle.

For sanitary napkins; 1 for lightly stained, 5 for moderately soiled and 20 for completely saturated pads.

Clots are given a score of 1 for small and 5 for large clots. For flooding a score of 5 is given also.

Possible range of total score is completely dependent on quantitative and qualitative amount of bleeding during menstruation. Abnormal PBAC score ≥ 100 , which correlates with menorrhagia, is defined as ≥ 80 ml of menstrual blood loss.

OBSERVATIONS AND RESULTS

Initially we recruited 52 patients for dienogest in which 41 patients completed study while 11 patients lost in follow up. In those 11 patients, 4 patients had gone through hysterectomy. The present study was conducted on 41 patients, The means age of patients were 32.88 ± 6.97 years and most of the patients (65.85%) from urban area. Most of patients in our study were literate (85.36%). Socioeconomic status of most of patients were middle class. Maximum number of the cases in the study were housewives(65.85%). In our study most of the women presenting with complaint of abnormal uterine bleeding were married, It was further observed in this study that as the parity increased, the abnormal uterine bleeding also increased. Effects of Dienogest treatment on Endometrial thickness, Haemoglobin and PBAC Score were seen in patients of Abnormal uterine bleeding.

Table 1: Effects Of Dienogest On Endometrial Thickness.

ENDOMETRIAL THICKNESS (MM)	DIENOGEST EFFECT
Pre treatment (Basal) (mean \pm SD)	8.73 ± 1.15
Post treatment at 3 months (mean \pm SD)	7.64 ± 1.05
Post treatment at 6 months (mean \pm SD)	6.80 ± 1.10
P value	$\leq .001$

The treatment effects of Dienogest in patients of abnormal uterine bleeding, it was found that the endometrial thickness (in mm) has decreased to 7.64 ± 1.05 at 3 months and 6.80 ± 1.10 at 6 months (post-treatment), from the basal value (pretreatment) of 8.73 ± 1.15 (mm). The decrease in endometrial thickness was statistically highly significant, on follow up (post treatment) at three months and six months, ($p < 0.001$, significant).

Table 2: Effects of Dienogest on Haemoglobin.

HAEMOGLOBIN	DIENOGEST EFFECT
Pre treatment (Basal) (mean \pm SD)	$8.19 \pm .96$
Post treatment at 3 months (mean \pm SD)	$8.79 \pm .94$
Post treatment at 6 months (mean \pm SD)	$9.63 \pm .90$
P value	$\leq .001$

The treatment effects of Dienogest in patients of abnormal uterine bleeding haemoglobin levels has increased to $8.79 \pm .94$ at 3 months and 9.63 ± 0.90 at 6 months (post-treatment) from the pretreatment (basal value) of 8.19 ± 0.96 (gm/dl). The increase in mean haemoglobin levels was highly significant statistically, on post treatment at three months and six months, ($p < 0.001$, significant).

Table 3: Effects of Dienogest on PBAC Score.

PBAC SCORE	DIENOGEST TREATMENT
Pre treatment (Basal) (mean \pm SD)	222.15 ± 51.15
Post treatment at 3 months (mean \pm SD)	142.80 ± 59.66
Post treatment at 6 months (mean \pm SD)	113.83 ± 46.34
P value	$\leq .0001$

The treatment effects of Dienogest, in patients of abnormal uterine bleeding it was found that PBAC score has decreased to 142.80 ± 59.66 at 3 months and 113.83 ± 46.34 at 6 months (post-treatment) from the basal value (pretreatment) of 222.15 ± 51.15 . The decrease in PBAC score was highly significant statistically, at three months and six months (post treatment), ($p < 0.001$, significant). Serious side effects which warrant discontinuation of drug were not seen with dienogest but few side effects like headache in 1(2.4%) patient, weight gain in 5(12.19%) patients, spotting in 4(9.76%) patients, and amenorrhoea in 3(7.32%) patients, nausea and vomiting in 1(2.4%) patient were obtained, also none of the patients in study group developed any significant alteration in liver or renal functions.

DISCUSSION

The normal menstrual cycle consists of 21-35 days, the blood flow lasts 2-7 days and the blood loss is about 20-80 ml in a cycle. The deviation in amount and duration from this normal is recognised as abnormal uterine bleeding. In our study we had seen the treatment effect of Dienogest in patients of abnormal uterine bleeding on Endometrial thickness, Haemoglobin and PBAC Score.

Dienogest is very effective improving all the parameters of blood loss in AUB including the no. of days of bleeding, no. of pads soiled and the passage of clots. In our study effect on endometrial thickness of 41 patients

was observed, A marked decrease in endometrial thickness in 3 months decrease in endometrial thickness was 12.48% while decrease in endometrial thickness was 22.11% in 6 months, Effect of dienogest on haemoglobin in our study that haemoglobin level rised significantly, it was increased 6.82 % in 3 months while 14.95% in 6 months.

PBAC score was reduced due to effect of dienogest in our study, decrease in PBAC Score was decreased 35.72 % in 3 months while 48.76 % in 6 months.

CONCLUSION

If we consider costs and complications of surgical treatments, medical therapy should always be tried first in cases of AUB. Medical management has always been the first therapeutic option to be tried and if it fails to show results, one can resort to surgical interventions. Hysterectomy should be the last resort in the management of AUB. The RCOG recommends beginning with medical management before resorting to surgical interventions. While hysterectomy offers an effective cure, it is suitable only for those, who have completed their family and Dienogest has the potential to be an effective treatment for AUB and it should always be considered amongst the all conservative treatment options. But it's main drawback is it's cost, so it can not be given to poor patients. Failure to respond to dienogest can be suggestive of some underlying organic pathology and patient needs to be re-evaluated for the same. Though conclusions from the study are limited by small number of subjects, and limited duration of study.

ACKNOWLEDGEMENT

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