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Effect of Ormeloxifene for Management of Dysfunctional Uterine Bleeding

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Abstract

Menorrhagia is an abnormal vaginal bleeding. Ormeloxifene is anti proliferative drugs which reduce production of various endometrial derived local factors and corrects menorrhagia with decrease menstrual blood loss (MBL) and clots. Therefore, we aimed to determine the effect of Ormeloxifene in women with dysfunctional uterine bleeding. We enrolled a total of 172 patients, aged 25 to 45 year, attended outpatient of gynecology department with complaints of heavy menstrual blood flow. Ormeloxifene was administered orally twice a week for first 12 weeks and then once in a week for next 12 weeks. MBL was measured using pictorial blood loss assessment chart (PBAC), blood hemoglobin. The median difference between pretreatment and post-treatment PBAC score was found to be significant. Similarly, It was also same with the difference in mean hemoglobin between pretreatment and post-treatment levels. The frequency distribution of clots during post treatment was significant as compared to pretreatment. Ormeloxifene is a cost effective effect therapy.

Keywords: Dysfunctional uterine bleeding; Ormeloxifene; Menorrhagia

Abbreviations: PBAC: Pictorial Blood loss Assessment Chart; MBL: Menstrual Blood Loss; ORs: Odds Ratios; 95% CI: 95% Confidence Interval

Introduction

Menorrhagia is abnormal vaginal bleeding from the genital tract in reproductive age group women [1-3]. It occurs due to disturbance in the menstrual cycle by regular and irregular uterine bleeding and alteration in the amount or duration of menstrual loss. It can cause hemorrhagic shock, anemia, iron deficiency and decrease quality of life [4]. The prevalence of menorrhagia is reported to be 30% in USA population [5]. However, till date there is no published report from Asian countries including India. It affects 10-30% of women at some stage in their life [1,6]. There is no definite pathology at hysterectomy in approximately 50% of cases [2]. The path-physiology of dysfunctional uterine bleeding is largely unknown but occurs in both ovulatory and anovulatory menstrual cycles [3]. A number of the local factors are thought to be involved in the local control of menstrual blood loss and abnormality in these factors that may cause menorrhagia [7]. However, the exact risk factors at the level of endometrial are unknown but it may occur due to imbalance in the menstruation mechanism.

The treatment of menorrhagia is a demanding task and various drugs like NSAID's, hormones; copper containing intrauterine device and endometrial ablation/resection are to be known. However, still hysterectomy is only available therapy. Ormiloxifene is one of the selective estrogens receptor modulators (SERM) [8] which binds with high affinity of estrogen receptors and mimics the effect of estrogen in some tissue. However, Ormeloxifene acts as estrogen antagonist in uterus (endometruim), breast tissues which lead to endometrial atrophy hence the decreases menstrual blood loss [9]. Therefore, the aim of present study to evaluate the effect of ormeloxifene drug in women with dysfunctional uterine bleeding.

Materials and Methods

Cases of dysfunctional uterine bleeding with age range of 25-45 years were randomly taken between July 2007 to December 2009 from the Department of Obstetrics and Gynecology, CHC, Sarai Akil, Allahabad, Uttar Pradesh. Women's with all parous (one or more), who did not wish to conceive further pregnancy, suffering for menorrhagia or polymenorrhagia, no clinical evidence of jaundice or hepatic dysfunction, polycystic ovarian disease and chronic cervicitis were included in the study. Women with presence of pregnancy, recent history of abortion, retained product of contraception, suffering from other pathology like fibroid, ovarian cyst or tumor, adenomyosis, cervical hyperplasia, genital malignancy, endometrial hyperplasia, systemic disease as platelet disorder/ coagulopathy, history of thrombosis or taking medication like heparin, use of intrauterine contraceptive device and suffering from medical illness like Jaundice/hepatic dysfunction were excluded from the study. Ormeloxifene is selected for this study.Ormeloxifene drug is cost effective and freely available in market named as Saheli (about 100 rupees of a month). The main side effect was hot flushes, prolong and scanty menses which was tolerable. No other major side effect was seen. Patients using this drug can be saved from abdominal surgeries/ LSCS.

The ormeloxifene drug was administered orally in the form of tablet (60 mg) twice weekly (Sunday and Wednesday) for first 3 months (12 weeks) and then once a week for another up to 12 weeks. Oral iron supplementation was given to mild and moderate anemic women and inject- able (iron/gm) was given to severe anemic women. At least two pretreatment baseline cycles were noted as per PBAC scoring. The study was approved by our hospital's research ethics committee and informed consent was obtained from each study participant. Menstrual blood flow, dysmenorrhea, any side effect of drugs, number of napkins used daily and degree of soiling of each pad used were recorded in a pre-designed questionnaire. Number and size of clots passed were also noted. Scoring was done on the basis of degree of soiling of pads, number of clots passed. Score ≥ 100 was considered as menstrual blood

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loss and ≥ 80 ml was considered diagnostic for menorhagia. Menstrual flows were categorized as normal, light, average, heavy and very heavy. Dysmenorrhea was categorized as absent, mild, moderate and severe. They were advised to attend four weekly or earlier if needed. All cases were North Indians.

All patients were undergone to detailed history (including age, parity, contraceptive history, obstetric history, last menstrual history, any abortion and medications), wish to retain uterus. They were examined in detail including general (jaundice, petechiae), systemic (any organomegaly) and gynecological examination (including per speculum and per vaginal examination for exclusion of any local pathology). The amount of MBL was assessed by asking the number of pads used by the patients, history of passage of clots during menstruation degree of soakage of sanitary pads and clinically by hemoglobin estimation. At least two pretreatment baseline menstrual blood losses were noted as per PBAC scoring. Basic investigations included blood complete picture, platelet count, bleeding time and clotting time. All patients underwent trans-vaginal sonography (TVS). The main outcome measures were menstrual blood loss, blood hemoglobin levels as studied by trans-vaginal sonography [10]. MBL was assessed prior and after treatment (>3 months) by using PBAC scoring [10]. Blood hemoglobin level and menstrual blood loss were measured initially and at the end of the study. Trans-vaginal sonography was done for exclusion of any uterine and adenexal mass and to measure endometrial thickness. The histopathology examination of endometrium (size >12 mm) in women's up to age of 45 years were done (Data not shown).

Data analysis

Age and parity variables were expressed as mean ± standard deviation (SD) and range. We used the Paired-samples T test to estimate the mean, median, range, p and t value. We also used the χ^2 statistic (Fisher's exact test for cell size <5) to compare frequency in presence of clot, dysmenorrhoea and amount of blood flows. The risks of average blood flow versus heavy and very heavy blood flow was estimated as odds ratios (OR) and 95% confidence intervals (CI) using χ^2 test. All statistical analysis were performed using SPSS software version 11.5 (SPSS, Chicago, IL, USA) and tests of statistical significance were two-sided and differences were taken as significant when *p*-value was less than 0.05.

Results

The study population consisted of 172 patients with dysfunctional uterine bleeding. The mean and range of age and parity of patients were 34.10 ± 5.207 (range 25-45) years and 3.65 ± 1.20 (range 7.00-1.00) respectively.

Outcome measurements

The different outcome measurements are shown in Table 1. The median pretreatment baseline PBAC score found to be 317.00 with a range of 125-768. The median post treatment PBAC score was 105.00 with a range of 3.0-557. The median decrease of 212 in post treatment PBAC score was statically significant (p = <0.0001, paired t = 10.14; 95% CI = 149.21-221.41).

The mean pretreatment Hb concentration found to be 8.89 gm/dl with a range of 6.40-11.20. The mean post treatment Hb concentration was 10.78 gm/dl with a range of 7.20-12.60. The mean increase of 1.89 in Hb concentration was statically significant (p = <0.0001, paired t = 1.25; 95% CI = 0.05-1.48). One seven tee two (100%) patients were anemic at initiation of the study as defined by World Health Organization (hemoglobin less than 12 gm/dl in non pregnant women) (WHO, 1968). One forty eight (86%) had significant anemia of hemoglobin less than 10 gm/ml. After three months of treatment, 162 (94.18%) patients were found to be less than 12 gm/ml hemoglobin and 10 patients (5.81%) were found to be hemoglobin less than 10 gm/ml.

The distribution of frequency of presence of clots during post treatment (18.6%) was found to be lower in compared to pretreatment (70.3%) and the difference was significant (p = <0.0001, paired t = 12.68; 95% CI = 0.59-0.43). The distribution of frequency of presence of dysmenorrhea during post treatment (18.6%) was lower in compared to pretreatment (26.2%) and the difference was insignificant (p = 0.067, paired t = 1.87; 95% CI = 0.15-0.004). Twenty four women continued to have heavy bleeding despite of taking drug. All were undergone to total hysterectomy. The incidence of hysterectomy was found to be 24/172 (13.95%).

Subjective assessment of amount of flow

Result showed reasonable improvement in amount of flow assessed subjectively by the drug users (Table 2), though 31 patients developed amenorrhea, 12 (38.70%) patients showed amenorrhea belongs to older (40 year or above age group) and 13 (41.93%) patients belongs to 35-39 years of age group and 6 (19.35%) patients belongs to 30-34 years of age group.

Parameters	Pre-treatment	Post-treatment	Remarks
Median PBAC score	317.00 (Range mini-max: 125-768)	105.00 (Range mini-max: 3.0-557)	t = 10.14, p = <0.0001; 95% CI = 149.21-221.41
Mean Hemoglobin level (gm/dl)	8.89 ± 0.94 (Range mini-max: 6.40-11.20)	10.78 ± 1.05 (Range mini-max: 7.20-12.60)	t = 1.25, p = <0.0001; 95% CI = 0.05-1.48
Presence of clots (Proportion of Subjects)	121 (70.3)	32 (18.6)	t = 12.68, p = <0.0001; 95% CI = 0.59-0.43
Dysmenorrhea (Proportion of Subjects)	45 (26.2)	12 (18.6)	t = 1.87, p = 0.067; 95% CI = 0.15-0.004

Table 1: Outcome measurements.

Amount of flow	Nil	Light	Average	Heavy	Very heavy
Pretreatment	0	0	39 (22.67)	102 (59.30)	31 (53.32)
Post treatment	31 (18.02)	36 (20.93%)	80 (46.51)	17 (9.88%)	8 (4.65)
OR* (95%CI) P value	# NC	# NC	1 (Reference)	0.07 (0.04-0.15) $1.0x10^{-6}$	0.13 (0.05-0.32) 0.9×10^{-6}

*χ^2 estimated OR (odds ratios) and 95%CI (confidence intervals) in average vs. heavy and very heavy; # NC= Not calculated

Table 2: Subjective assessment of amount of flow.

Discussion

Menorrhagia is socially embarrassing, physically incapacitating condition and has great financial drain. In this study, PBAC score was found to be significantly decreased in patients of post-treatment using ormeloxifene drug. Since ormeloxifene drug have anti-proliferative effect on uterus (endometruim) which causes endometrial atrophy and that may resulting in decrease of menstrual blood loss, hence causes decrease in PBAC score. Our results are comparable with the study done in Indian population from Darjeeling and New Delhi by Biswas et al. [11] and Kriplani et al. [12].

In the present study, hemoglobin level showed significantly increased in patients of post treatment after using ormeloxifene drug. It is because, ormeloxifene act as antagonist effect on estrogen receptors of uterine endometrium, which decrease the stimulation of receptor activity of uterine and causes their prolonged depletion on uterus. Therefore, it may decrease the uterine bleeding and may increase the hemoglobin level. Biswas et al. [11] has also reported similar result in Indian population and showed average increase of 1.31 gm/dl in Hb concentration. Our study observed significant decrease in the presence of clots in patients of post-treatment after using ormeloxifene drug. Presence of clots is an obvious evidence of abnormal excessive menstrual blood flow [10]. We postulated that ormeloxifene has anti-proliferative activity on uterine endometrium which causing endometrial atrophy and it may reduce menstrual blood flow and decrease of clots in the blood at the end of therapy. A study also showed improvement by absence of clots in 85.71% patients [11].

In the present study, the improvement was observed by absence of dysmenorrhea in patients of post-treatment after using ormeloxifene drug which acts by blocking the action of progesterone. It is seen that only ovulatory cycles are associated with dysmenorrhea. It occurs due to increase uterine tone and spasmodic contraction as a consequence of uterine muscular activity [13]. Myometrial contraction are thought to be stimulated by prostaglandins specially PGF2 (prostaglandin F2-alfa) and other local factors like vasopressin and endothelins [14], released by endometrium during menstruation [15]. Optimal level of estrogen is necessary or action of progesterone. So, high level of progesterone through increase the level of various prostaglandins especially prostaglandin F2-alfa (PGF2) causes pain during menstruation known as dysmenorrhea. Similar results were also shown by other studies done in Indian population [11].

In this study, we observed decrease of blood flows in heavy and very heavy patients of post-treatment after using ormeloxifene drug. Since, Ormeloxifene acts as antagonist effect of estrogen receptors on uterus (endometruim), it will reduce the stimulation of estrogen receptors. Hence, it may have reduction in amount of blood flows. Our result is supported by the earlier study [11].

In summary, the treatment of Ormeloxifene in patients with dysfunctional uterine bleeding is significantly increasing the level of hemoglobin by decreasing the clots and PBAC score. These results conferred that the drug has an excellent safety profile and has been found to have very few side effects.

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