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ORIGINAL RESEARCH

Comparison of effectiveness of ormeloxifene with norethisterone in abnormal uterine bleeding

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Abstract

Introduction: Abnormal uterine bleeding is defined as ‘‘bleeding from the uterine corpus that is abnormal in volume, regularity, and/or timing’’Menorrhagia is socially embarrassing, physically incapacitating condition and has great financial drain. About 10-15 % of women experience episodes of abnormal uterine bleeding at sometime during the reproductive years of their life. Its common during extremes of reproductive life, following pregnancy and during lactation.

Material and Methods: The present study was undertaken to evaluate and compare the effect of ormeloxifene as compared to norethisterone on PBAC score , hemoglobin and endometrial thickness and any side effect arising out of their use. The present study was carried out in 70 women of age 25 to 40 years with complain of heavy and prolonged menstrual bleeding attending out patient and in patient department of Obstetrics and Gynaecology at VALASMC, Etah . The cases were randomly allocated to two groups. Group 1- included 31 cases who received ormeloxifene 60 mg twice a week for 12 weeks followed by 60 mg once a week for next 12 weeks & Group 2- included 32 cases who received 5 mg norethisterone twice daily for 21 days for 6 consecutive cycle.

Results: After six months of Ormeloxifene treatment , mean hemoglobin increased from 8.1 gm/dl to 10.2 gm/dl. This increase was statistically significant (P< 0.0001. With Norethisterone, mean hemoglobin increased from 8.2 gm/dl to 9.6 gm/dl after six months of treatment. This increase was statistically significant (P< 0.0001). After three months of treatment with Ormeloxifene, mean endometrial thickness was decreased from 8.9 mm to 7.1 mm. This decrease was statistically significant (P< 0.0001). With Norethisterone, mean endometrial thickness was decreased from 9.1 mm to 8.1 mm after three months of treatment. This decrease was statistically significant (P< 0.0001). After six months of Ormeloxifene treatment, mean endometrial thickness was decreased from 8.9 mm to 6.1 mm. This decrease was statistically significant (P< 0.0001). After six months of Norethisterone treatment, mean endometrial thickness was decreased from 9.1 mm to 7.2 mm. This decrease was statistically significant (P< 0.0001)

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Conclusion: Thus it was concluded from the present study that both drugs were effective in treating abnormal uterine bleeding. . In the study Ormeloxifene was found to be effective than Norethisterone in reducing blood loss, improving Haemoglobin level and reducing endometrial thickness for treating AUB patients. Also compliance of the patients was good because drug was well tolerated, convenient dosage schedule for treatment of AUB.It can be used in any age group and is oncologically protective to the breast and endometrium

Introduction

Disorders of menstruation account for the most common reason for a gynaecological consultation among women of reproductive age group. Abnormal uterine bleeding is one such condition most commonly affecting women from extremes of reproductive age group. Abnormal uterine bleeding is defined as ‘‘bleeding from the uterine corpus that is abnormal in volume, regularity and/or timing’’.About 10-15 % of women experience episodes of abnormal uterine bleeding at sometime during the reproductive years of their life. Abnormal uterine bleeding can occur at any time between menarche and menopause in ovulatory or anovulatory cycles. The latter tends to be more common at puberty and after the age of 40, times at which irregular ovulation is often encountered. Altered hypothalamic – pituitary- ovarian function and /or local changes in prostaglandins production can give rise to abnormal uterine bleeding. It is typically characterized by heavy and prolonged flow with or without breakthrough bleeding[1]. The treatment options for dysfunctional uterine bleeding are diverse, which can be finally tailored to cater the needs of patients of different socioeconomic background, different age groups and different reproductive needs[2] . Treatment modalities available include medical therapy and surgical interventions. Various pharmacological agents used in treatment of AUB are combined oral, progestogens, danazol, Gn RH agonists, PGsynthetase inhibitors, antifibrinolytics and ethamsylate[3]. Medical management has always been the first therapeutic option to be tried. Hysterectomy should be the last resort in the management of AUB. Because of the morbidity associated with the surgical procedures, the ACOG recommends beginning with medical management before resorting to surgical interventions[4]. Medical treatment of menorrhagia should aim to relieve symptoms, improve quality of life and avoid the risk of surgery. Norethisterone is still the most frequently prescribed drug, serving 38% of the patient population, the reason being cost effectiveness and lesser side effects[5].Ormiloxifene is one of the Selective Estrogens Receptor Modulators (SERM) which binds with high affinity to estrogen receptors and mimics the effect of estrogen in some tissues but act as estrogen antagonist in others[6]. It is also popularly known as centchroman. It acts as estrogen antagonist in uterus (endometrium) which leads to endometrial atrophy hence decreases menstrual blood loss.The present study was undertaken to evaluate and compare the effect of ormeloxifene as compared to norethisterone in abnormal uterine bleeding.

Material and Methods

This prospective study was carried out on 70 women of age 25 to 40 years attending out patient department and indoor cases of Department of Obstetrics and Gynaecology, VALASMC, Etah. Women between 25 and 40 years of age with complain of heavy and prolonged menstrual bleeding were recruited for the study. The exclusion criteria were pelvic pathologies like uterine fibroids, suspected adenomyosis, malignancies of uterus/ cervix/ ovary/ vagina/ endometrial hyperplasia with atypia; medical diseases– liver dysfunction, heart disease, migraine, stroke, renal disease, hypo/hyperthyroidism, platelet disorders or coagulopathy, previous history of thrombosis, pregnancy, abortion, use of IUCDs or oral contraceptives, lactating women in first 6 months of post-natal period, hypersensitivity to the drug. The cases were divided into two groups. **Group 1-** included those cases who received ormeloxifene 60 mg twice a week for 12 weeks followed by 60 mg once a week for next 12 weeks & **Group 2-**

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included cases who were given 5 mg norethisterone twice daily for 21 days for 6 consecutive cycle. Informed consent was taken. A thorough systemic, gynaecological examination and routine investigations including hemoglobin and endometrial thickness by USG were done at first visit. Follow up was done at 3 months and 6 months or earlier if needed. Menstrual blood loss was measured objectively by a pictorial blood loss assessment chart (PBAC) score as described by Higham et al[7]. The women were asked to maintain menstrual calendar and use certain sanitary products which have been shown to have similar absorbent capacities .Scores were assigned to different degree of soiling of sanitary products and number and size of clots passed Table. 2 PABC score of greater than or equal to 100 indicates menstrual blood loss greater than or equal to 80 ml and is considered diagnostic for menorrhagia. The primary outcome measures were menstrual blood loss, hemoglobin concentration and endometrial thickness.

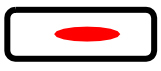
Observations and Results

Out of 70 patients enrolled, 63 completed the study and 7 lost the follow-up. Age of the treated patients ranged between 25 to 40 years and maximum number of patients were in the age group between 30 to 35 years (73.01%). Menstrual blood loss (assessed by PBAC score), hemoglobin level and endometrial thickness were observed before starting treatment and then after 3 and 6 months of treatment. The outcome measures at 3 months and at 6 months are shown in Table 3,4 & 5.In group 1, mean PBAC score before treatment was 244.2, which was decreased significantly to 65.7 after 6 months of treatment with ormeloxifene. The mean pretreatment PBAC score in group 2 was 237.5 which reduced to 85.3 after 6 months of therapy . In group 1, mean hemoglobin level before treatment was 8.1 gm%, which was increased significantly to 10.2 gm% after 6 months of treatment. The mean pretreatment hemoglobin level in group 2 was 8.2 gm% which was increased to 9.6 gm% after 6 months of therapy. Table 5 shows the comparison of reduction in mean endometrial thickness among the two groups. In group 1, mean endometrial thickness before treatment was 8.9 mm, which was reduced significantly to 6.1 mm after 6 months of treatment. The mean pretreatment endometrial thickness in group 2 was 9.1 mm which was decreased to 7.2 mm after 6 months of therapy. Serious side effects which warrant discontinuation of drug were not seen in any group. Amenorrhea was the most common symptom in Group 1, seen in 17 women. However some or other side-effects were seen in few patients as shown in Table 6.

TABLE -1: DISTRIBUTION OF CASES

	DRUG USED	NO. OF CASES	PERCENTAGE
1.	Ormeloxifene	31	49.2 %
2.	Norethisterone	32	50.8 %
Total		63	100%

TABLE -2: PBAC SCORING

Pads		
1point	For each lightly stained pad	
5points	For each moderately stained pad	
20points	For each completely saturated pad	

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Clots/Flooding		
1point	For each small clot(Australian 5cent coin)	
5points	For each large clot(Australian 50cent coin)	
5points	For each episode of flooding	

TABLE–3: PBAC SCORE PRE TREATMENT, AT 3 MONTHS AND AT 6 MONTHS

GROUPS/PBAC SCORE	GROUP-1 (n=31)	GROUP-2 (n=33)
PRE TREATMENT PBAC SCORE MEAN	244.2	237.5
PBAC SCORE MEAN AT 3 MONTHS	133.7	142.2
PBAC SCORE MEAN AT 6 MONTHS	65.7	85.3
P VALUE WITHIN SAME GROUP	<0.0001	<0.0001

TABLE-4: HAEMOGLOBIN(gm/dl)

GROUPS/ HAEMOGLOBIN	GROUP-1 (n=31)	GROUP-2 (n=33)
PRE TREATMENT	8.1	8.2
MEAN AT 3 MONTHS	8.8	8.6
MEAN AT 6 MONTHS	10.2	9.6
P VALUE WITHIN SAME GROUP	<0.0001	<0.0001

TABLE-5: ENDOMETRIAL THICKNESS(mm)

GROUPS/ ENDOMETRIAL THICKNESS	GROUP-1 (n=31)	GROUP-2 (n=33)
PRETREATMENT MEAN	8.9	9.1
MEANAT3 MONTHS	7.1	8.1
MEANAT6 MONTHS	6.1	7.2
PVALUEWITHIN SAMEGROUPS	<0.0001	<0.0001

TABLE-6 : SIDE EFFECT PROFILE OF THE DRUG

SIDE EFFECTS	GROUP-1	GROUP-2
NAUSEA& VOMITING	0	2
WEIGHT GAIN	0	2
HEADACHE	1	5
SPOTTING	1	4

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AMENORRHEA	17	0

Discussion

There are varieties of treatment available for abnormal uterine bleeding, from medical therapy to minimally invasive surgery to conventional hysterectomy. However, medical treatment should be the preferred modality of treatment when possible.In this study maximum numbers of cases (73.01 %) were of age group 31 to 35 years age. Parity of patients was comparable in all the three groups.. In this study the Pictorial Blood loss Assessment Chart (PBAC) Scoring was done accordingly to assess menstrual blood loss. In Group-1 decrease in mean PBAC score was found to be extremely significant (P< 0.0001) which was reduced from 244.2 to 65.7 after 6 months. Mean PBAC score in Group-2 was reduced from 237.5 to 86.3 at six months which was also significant (P< 0.0001). **Shreya et al (2015)** noted significant decrease in PBAC Score after treatment with ormeloxifene. A favorable decrease similar to our study was noted in mean PBAC score from 320 to 60 (p<0.001)[8]. **Chitrangada et al (2014)** recorded in their study similar reduction in mean PBAC score with ormeloxifene (196.46 to 79.57) and it was significantly more than seen with norethisterone (186.35 to 105.76)[9]. **Shazia et al (2014)** noted similar results to our study recording significant increase in hemoglobin concentration from 8.1 to 9.4 gm/dl with a rise of 1.3 gm/dl (p<0.05) after treatment with ormeloxifene[10].Our results were also comparable with the results of **Jacob KJ et al (2015)[11]**. The increase in hemoglobin levels were found to be more significant with ormeloxifene than norethisterone in their study (9.68 gm% to 11.07gm% vs. 10.17gm% to 10.58 gm% respectively, p value <0.05).In our study the endometrial thickness before treatment in Group 1 and Group 2 were 8.9 mm and 9.1 mm respectively which were comparable to each other. Significant reduction in endometrial thickness was noted in both groups. After six months endometrial thickness in Group 1 & Group 2 was reduced to 6.1 mm and 7.2 mm respectively which was statistically significant (p<0.001).In the study done by **Surabhi HD et al (2019)** mean pretreatment endometrial thickness was reduced from 7.4 mm to 5.1 mm with ormeloxifene (p<0.0001) Haemoglobin levels reported statistically increase in both groups with p value less than 0.001. Ormeloxifene reported more rise in haemoglobin when compared with norethisterone as comparable to our study[12]. **Chitrangada et al(2014)** showed in their study that the initial average endometrial thickness was 5.49 in Ormeloxifene Group and 5.08 in Norethisterone group. The endometrial thickness changed to 4.49 in case of Ormeloxifene and 4.83 in case of Norethisterone, showing a significant decrease in the former compared to later and the inter group variation was significant. These findings are similar with the results of our study[9].

Conclusion

It was concluded from the present study that both drugs were effective in treating abnormal uterine bleeding. Even though the treatment with Norethisterone had good results, our study concludes Ormeloxifene as more effective drug for treatment of AUB. In the study Ormeloxifene was found to be effective than Norethisterone in reducing blood loss, improving Haemoglobin level and reducing endometrial thickness for treating AUB patients. It has a 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 the breast and endometrium.

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