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Role of Ormeloxifene in the Treatment of Dysfunctional Uterine Bleeding.

KEYWORDS: Dysfunctional Uterine Bleeding (DUB). Pictorial blood loss assessment chart (PBAC)

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ABSTRACT *Introduction: Dysfunctional uterine bleeding (DUB) is a state of abnormal uterine bleeding without any clinically detectable organic, systemic and iatrogenic cause. It is the most common menstrual disorder of women in reproductive age and is a diagnosis of exclusion.*
Aims and Objectives: The aim of the present study is to evaluate the efficiency and safety of Ormeloxifene in Dysfunctional Uterine bleeding.
Method: This prospective study was conducted in the Dept of Obstretics and Gynaecology JLNMCH, Bhagalpur over a period of 1 year from Jan 2015 to Dec 2015. The Diagnosis of Dysfunctional Uterine bleeding was grade after excluding possible causes of abnormal uterine bleeding. 50 patients of DUB were recruited from OPD. Two pre treatment cycles were compared with six consecutive treatment cycles of Ormeloxifene. All cases were given Ormeloxifene twice a week for 3 months then once a week for another 3 months. Follow up was done at 3 months and 6 months. Main outcome measures were menstrual blood loss.
Result: Almost all patients had PBAC score less than 100, thus no menorrhagia following treatment. 11 patients developed amenorrhoea which is the most common side effect of Ormeloxifene. 82% of patients had decrease in endometrial thickness by more than 0.5 mm. Almost all patients had increase in haemoglobin level following treatment. Side effects seen during treatment were G.I side effects, headache, Amenorrhoea.
Conclusion: Ormeloxifene is well tolerated and safe alternative for medical management of Dysfunctional uterine bleeding.

INTRODUCTION:

Dysfunctional uterine bleeding (DUB) is a state of abnormal uterine bleeding without any clinically detectable organic, systemic and iatrogenic cause. It is the most common menstrual disorder of women in reproductive age and is diagnosis of exclusion. It can affect any woman from menarche to menopause, occurring more commonly at extremes of age. Menorrhagia (menstrual blood loss > 80 ml/ cycle or PBAC score > 100) affects 10-33&% of women at some stage in their lives[2].

Medical management of menorrhagia is a challenging task. Wide variations in the available drugs prescribed for this condition shows a lack of consensus for medical management[2]. The medical opinions for initial management of DUB include antifibrinolytics, non steroidal anti inflammatory drugs, Combined estrogens & progesterone or progesterone alone, high dose estrogens. Gonadotropin-releasing hormone agonists danazol and Levonorgestrol releasing intrauterine systems. Cyclical OCPs were widely used previously but side effects have limited their use in DUB. Danazol, progesterone and Gonadotropin- releasing hormone analogs are all effective in terms of reducing menstrual blood loss but adverse effect and costs limit their long term use[28].

Selective Estrogens Receptor Modulators (SERMs) selectively bind with high affinity to estrogens receptors and act as estrogen agonists in some tissues and estrogen antagonists in others.

Ormeloxifene, a 3rd generation SERM, antagonises the effect of estrogen on uterine & breast tissue and stimulates its effect on vagina, bone, cardiovascular and central nervous system[25].

Thus it is especially beneficial in perimenopausal women. It has additional advantage of reducing premenstrual symptoms, mastalgia and dysmenorrhoea.

AIMS & OBJECTIVES

The aim of the present study is to evaluate the efficacy and safety of Ormeloxifene in Dysfunctional uterine bleeding.

MATERIAL AND METODS

This prospective study was conducted in the Department of Obstretics and Gynaecology, Jawaharlal Nehru Medical College & Hospital, Bhagalpur over a period of 1 Year from January 2015 to Dec 2015. Fifty Pts were recruited from gynaecological OPD. The diagnosis of dysfunctional uterine bleeding was made after excluding other possible causes of abnormal uterine bleeding.

Inclusion Criteria:
Patients included in the study were
Women aged 30-51 yrs with the diagnosis of DUB.

Multiparous women who do not want to conceive further.

Women willing to come for follow up and compliant to the treatment.

Exclusion Criteria:
Presence of pelvic pathology such as uterine fibroid, adenomyosis, malignancy of uterus, cervix, ovary, vagina.

Endometrial hyperplasia with atypia.

Systemic disease such as platelet disorder or coagulopathy.

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Previous history of thrombosis.

Pregnancy or willing for conception.

Consistent use of OCPs or NSAIDs.

Lives dysfunction.

Heart disease.

Migraine.

Stroke

Renal disease

Hypo / hyperthyroidism

History of recent abortion

Use of IUCDs

Lactating women in first 6month of post natal life

Hypersensitivity to the drug.

Informed consent was taken.

Two pre-treatment baseline cycles were compared to three to six consecutive treatment cycles of Ormeloxifene. All cases were given Ormeloxifene 60 mg twice a week for 12 weeks and then once a week for next 12 weeks. The drug was administered orally in the form of tablet SEVISTA (60 mg), Torrent pharmaceuticals Ltd, twice in a week on Tuesday and Friday for 1st 12 wks and then every Tuesday for another 12 weeks if required.

Follow up was done at three months and six months or earlier if needed. The main outcome measures were menstrual blood loss, blood haemoglobin level and endometrial thickness in proliferative phase as studied by Trans Vaginal Sonography.

Pictorial blood loss assessment chart (PBAC) [11], a method that correlate well with alkaline ratio and was used to measure the menstrual blood loss. A PBAC score[11] greater than or equal to 100 was considered menstrual blood loss greater than or equal to 80 ml and was thus diagnostic of menorrhagia.

Blood haemoglobin in gm/dl and endometrial thickness by TVS were measured initially and at the end of study. A well designed questionnaire recorded at the subjective assessment of menstrual flow and dysmenorrhoea and or any side effect of the drug. Menstrual flow was categorised as light, normal or average, heavy & flooding. Dysmenorrhoea was categorised as absent, mild, moderate and severe.

Continuous efficacy parameters were presented as mean ± SD and median (range) and were analysed using paired 'T' test. Statistical significance was taken as $P \leq 0.05$.

PBAC SCORE

PADS	Lightly soiled	01
	Moderately soiled	05
	Saturated	20
CLOTS	Small(Smaller than a rupee coin)	01
	Large(larger than a rupee coin)	05

RESULTS AND OBSERVATION:-

In this study a total of 50 pts were studied. Maximum number of pts before taking treatment had PBAC score above 100 thus belonging to category of menorrhagia. And those with lesser PBAC score had irregular menstrual cycle.

Table: 1.
No. of patients with their pre treatment PBAC score.

Serial. No.	PBAC score	No. of pts.
1.	< 90	04
2.	91-140	06
3.	141-190	10
4.	191-230	13
5.	231-270	08
6.	> 270	09

Table: 2. No. of patients with their post treatment PBAC score.

PBAC Score	No. of pts.
Amenorrhoea	11
< 40	11
40-90	23
> 90	05

Almost all patients had PBAC (Pictorial blood loss assessment chart) less than 100, thus no menorrhagia following treatment. 11 pts (22%) developed amenorrhoea which is most common side effect of Ormeloxifene.

Maximum number of patients had decrease in PBAC score by more than 100, thus bringing them in the range of normal menstrual blood loss.

Table: 3. Number of patients with their improvement in Hb (gm /dl) after treatment.

Serial No.	Post treatment Hb (gm/dl)	No. of patients
1.	< 0.5	11
2.	0.5 – 1	13
3.	1.1 – 1.5	14
4.	1.6 – 2.0	06
5.	> 2.0	06

Almost all patients had increase in haemoglobin level following treatment, 52% of pts had increase in Hb (gm/dl) by more than 1gm/dl.

Table: 4. No. of patients with their decrease in endometrial thickness following treatment.

Serial No.	Decrease in Endometrial Thickness (mm)	No of Patients
1.	< 0.5	09
2.	0.5 – 1	30
3.	> 1	11

So, 52% of patients had decrease in endometrial thickness by more than 0.5mm.

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Table. 3
Table: 5. Outcome measurements following 6 months of treatment.

Sl no.	Outcome parameters	Pre treatment	Post treatment	Remarks
1.	Median PBAC score	205	58	P=0.019, T=16
2.	Mean Hb ± S.D	7.7 ± 0.99 Gm/dl.	8.6 ± 0.95	P=.028, T=11
3.	Mean E.T ± S.D	9.37 ± 2.03 mm.	8.1 ± 1.10	P=0.0028, T=5
4.	Presence of clots	44/50	2/50	P<0.05
5.	Dysmenorrhoea	26/50 (12-mild,7-Mod, 7-Severe)	11/50 (8-mild, 3-mod)	P<0.05

Complications following six months of treatment.

Serial No.	Side effects	No. of patients	Percentage
1.	G.I Side effect	02	04%
2.	Headache	01	02%
3.	Amenorrhoea	11	22%
4.	Failure, followed by hysterectomy.	06	12%

DISCUSSION:
The median decrease in PBAC score in the present study is 136. The median decrease in PBAC score in the study done by Biswal Subhash Chandra, Saha Sandip Kumar, Bag Tara Shankar, Ghosh Roy Samir Chandra, Roy Ashit Chandra and Kabiraj Shankar Prasad in the year 2004 was 164: 2.

The median decrease in PBAC score after 6 months of treatment in the study done by Dr. Neha Agrawal & Dr. Saroj Singh in the year 2010 was 302.

The median decrease in PBAC score in the study done by Tapan Kumar Bhattacharya and Anusuya Banerjee in the year 2011 was 46: 12.

So, there is significant decrease in PBAC score following treatment and the result of present study is consistent with other studies mentioned above.

Table 3. Shows no. of patients with their improvement in Hb level following treatment. The mean increase in Haemoglobin level following treatment is 1.23gm/dl.

The mean increase in haemoglobin level following treatment in the study done by Biswal Subhash Chandra, Saha Sudip Kumar, Bag Tara Shankar, Ghosh Roy Samir Chandra and Kabiraj Shankar Prasad in the year 2004 was 1.31 gm/dl.

The mean increase in haemoglobin level following treatment in the study done by Dr. Neha Agrawal and Dr. Saroj Singh in the year 2010 was 1.82gm/dl.

The mean increase in haemoglobin level in the study done by Tapan Kumar Bhattacharya and Anusuya Banerjee in the year 2011 was 2.54gm/dl.

The mean increase in haemoglobin level following treatment in the present study is in accordance to other studies.

Table 4. Shows the mean decrease in endometrial thickness following treatment which is 1.19 mm with a range from 2.9 mm.

The mean decrease in endometrial thickness in the study done by Biswal Subhash Chandra, Saha Sudip Kumar, Bag Tara Shankar, Ghosh Roy Samir Chandra, Roy Ashit Chandra and Kabiraj Shankar Prasad in the year 2004 was 3.6 mm.

The mean decrease in endometrial thickness following treatment in the study done by Dr. Neha Agrawal and Dr. Saroj Singh in the year 2010 was 3.12mm.

The mean decrease in endometrial thickness following treatment in the study done by Tapan Kumar Bhattacharya and Anusuya Banerjee in the year 2011 was 1.158 mm.

The mean decrease in endometrial thickness following treatment in the study done by Dhananjay BS and Sunil Kumar Nanda in the year 2012 was 3.47 mm.

So, the decrease in endometrial thickness in the present study following treatment is consistent with other studies done on Ormeloxifene for Dysfunctional uterine bleeding.

OUTCOME MEASURES: Table (5)
Final outcome in the present study is a median decrease in PBAC score (pre treatment 205 to post treatment 58) with t = 16.0 and p = 0.019 (p<0.05).Thus significant Increase in mean haemoglobin (pre treatment 7.73 to post treatment 8.6 gm/dl) with t = 11 and p = 0.028 (p<0.05) thus significant. Decrease in mean endometrial thickness (pre treatment 9.37 ± 2.03 to 8.1 ± 0.95) with t = 5 and p = 0.0028 (p<0.05). 88% of patients had complain of passage of clots prior to treatment which reduced to 4% of patients following treatment with p = 0.03(p <0.05) thus significant 52% of patients had complain of dysmenorrhoea prior to treatment which was reduced to 22% following treatment with p = 0.04 (p < 0.05) thus significant. These results are consistent with other studies.

Table (6) shows complications or side effects of the treatment. Two out of 50 (4%) has gastrointestinal side effect. 1 out of 50 (2%) had complaint of headache. 22% of patients developed amenorrhoea, which is the most common complication seen in all studies of Ormeloxifene. 6 out of 5 patients were subjected to hysterectomy.

In the study done by Biswal Subhash Chandra, Saha Sandeep Kumar, Bag Tara Shankar, Ghosh Roy Samir Chandra, Roy Ashit Chandra and Kabiraj Shankar Prasad in the year 2004. 2.1% of patients had gastrointestinal symptoms, 1.17% patients had giddiness and amenorrhoea was noted in 17.64% of patients. 8.2% of women had to undergo hysterectomy.

In the study done by Dr. Neha Agarwal and Dr. Saroj Singh in the year 2010. 6.67% of patients had headache and 28.3% of patients developed amenorrhoea.

Other studies have not enumerated the side effect along with the percentage of patients in whom it was noticed.

The side effect complained by the patients in the present study is consistent with the other studies.

SUMMARY AND CONCLUSION:
Ormeloxifene is effective, quick acting and appears to be

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a promising option for the management of dysfunctional uterine bleeding. It leads to significant reduction in menstrual blood loss, a significant rise in haemoglobin concentration and a significant decrease in endometrial thickness without any major side effect. It has convenient dose schedule of one or twice a week and is cost effective. It can be used in any age group and oncologically protective to the breasts and endometrium. It is well tolerated and safe alternative for medical management of dysfunctional uterine bleeding.

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