



Comparative study of effectiveness of Ormeloxifene and Medroxy Progesterone Acetate in the management of Dysfunctional Uterine Bleeding

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Abstract

Abnormal uterine bleeding without any systemic or local structural causes was earlier termed dysfunctional uterine bleeding. It is nearly equivalent to COE of the new FIGO classification of AUB. Ormeloxifene is a non steroidal, nonhormonal, selective receptor modulator inhibitor, widely used as an oral contraceptive. In the past decade, Ormeloxifene was well established in the control of menorrhagia. This is a prospective, randomised, comparative study of the efficacy of Ormeloxifene and Medroxy Progesterone Acetate (MPA) in the control of bleeding in DUB. A group of sixty women, had Ormeloxifene 60 mg twice a week for 12 weeks and once a week for a further 12 weeks. Another group of sixty women, had MPA 20 mg a day cyclically for 21/28 days for six months. Hb level, endometrial thickness and PBAC score are the parameters analysed. In both groups, there is a significant improvement in Hb level. In control of bleeding, the action of Ormeloxifene is seen in a month and the benefit continued throughout the treatment. With MPA, the control of bleeding is not satisfactory in the first cycle, but from second cycle, there is satisfactory control of bleeding, slightly less than that of Ormeloxifene. During the course of treatment, 1/4th of women in Ormeloxifene group and 1/8 th of women MPA group became amenorrhic.

Keywords: AUB; DUB; Menorrhagia; Ormeloxifene; Medroxy progesterone acetate.

Introduction

Abnormal uterine bleeding (AUB) is any bleeding from the uterus which is not normal cyclical menstruation. It is a symptom, not a diagnosis. Excessive bleeding in amount or duration is a cause of worry to the patient and the clinician. Dysfunctional uterine bleeding is an earlier diagnostic term used when there is no systemic or locally definable structural cause of AUB. It is a

diagnosis of exclusion. Women who fit this description, generally have one or a combination of coagulopathy, disorder of ovulation and primary endometrial disorder — the COE of PALM COEIN of FIGO⁽¹⁾. DUB is a common debilitating problem accounting for 20% of all gynaecological consultations⁽²⁾.

The treatment modalities for DUB are A). Surgical- therapeutic D&C, Hysterectomy ;B). Medical –NSAIDs, anti fibrinolytics,

progesterone, levonorgestrel intra uterine system, combined oral contraceptives, danazol, GnRH. The choice of treatment depends on the age of the patient, fertility status and the severity of bleeding. The ideal drug should be, easy to use, cost effective, patient friendly, long lasting result if not permanent result, without much side effects. None of the drugs used have all these beneficial qualities,

Ormeloxifene popularly called Centchroman is a Selective Estrogen Receptor Modulator (SERM). It is estrogenic in some structures like bones and anti estrogenic in other parts like uterus and breast⁽³⁾. It is widely used as a non hormonal, non steroidal oral contraceptive under the trade names- Saheli, Centron, Sevista. It causes an asynchrony between ovulation and development of endometrium⁽⁴⁾. In the past decade, it has established itself as a safe and effective drug in the management of menorrhagia⁽⁵⁾.

Cyclical use of progestones like norethisterone and Medroxy Progesterone Acetate (MPA) is a safe and effective therapy for regularisation of cycles and for the control of menorrhagia⁽⁶⁾. The disadvantage is, it has to be used cyclically, 21/28 or 10-12/28 days regularly. In women in the 4th decade of life, its effect on glucose metabolism has to be looked into. Centchroman is used twice a week for three months, later once a week, which is a patient friendly dose.

In this study, an attempt is made to establish the efficacy of centchroman and MPA (A) in the management of menorrhagia in DUB, and B) to compare the efficacy of the two drugs objectively and subjectively.

Aim and Objective

To compare the efficacy of Centchroman and Medroxy Progesterone Acetate in control of bleeding in women with DUB

Material and Methods

The study was conducted by the authors in their parent institution and in their private consultation chambers in a city in Pondicherry state during the

period January 2014 to June 2019. Women who completed their child bearing function, sterilised or not; having menorrhagia for some months are the subjects of the study. DUB was confirmed by exclusion of all other causes of AUB. Women >45 years of age; history of cancer of uterus or breast in the family; women who underwent breast or upper genital tract operations earlier; who had a hormonal treatment in the past three months; endometrial thickness more than 15 mm; having a liver disease, thromboembolic disease, migraine-are excluded from the study.

Women who are willing to continue medical treatment for DUB for six months were only enrolled for the study. Discontinuation of the treatment and switching over to another mode of treatment, if necessary, in these six months was discussed with the patient. Ethical committee clearance and informed consent of the patient was obtained. Women with DUB were examined clinically, necessary investigations and premenstrual ultrasonography for endometrial thickness was done. Endometrial sampling was done by Pipelle in all women. Pictorial Blood loss Assessment Chart (PBAC) was done by the patient in the earlier menses before drafting into the treatment and also in the cycle of initiation of the treatment—there by having a treatment free observational period of a month.

The women were allotted randomly to two groups— Group A, having Centchroman 60 mg twice a week on fixed days Sunday and Wednesday for 12 weeks (though centchroman can be started on any day of cycle, we started in the menstrual phase of first treatment cycle for convenience and comparison) and once a week for the next 12 weeks. Group B having Medroxy Progesterone Acetate 20 mg daily from 5th day to 25th day of every cycle for six menstrual cycles. The women were followed up every month for three months and later at the end of six months. PBAC was maintained by the patient. Endometrial thickness was done by TVS premenstrually. At every visit, weight gain, Hb level, FBS, patient's satisfaction

about the treatment and her subjective assessment of control of bleeding was enquired.

Results

A total of 76 women were drafted into group A, to get 60 women who completed the course for six months as per the protocol. In group B, 84 women has to be recruited to get 60 women to complete the course. In group A, one woman opted for hysterectomy on own, five women lost for follow up in the initial three months. Seven women lost for follow up at 24 weeks, three women

underwent hysterectomy--two patient initiated and one doctor suggested. In group B eight women discontinued treatment in the initial 12 weeks, (understandably when the bleeding control was not to their satisfaction), one underwent therapeutic D&C for control of bleeding; at 24 weeks, ten women lost for follow up; five women underwent hysterectomy--two indicated and three patient initiated. 84 women started the treatment and 60 women completed the treatment as per protocol.

Table 1

Parameter	Group A: N= 60	Group B: N= 60
Initiation of treatment	76	84
Lost for follow up or discontinued treatment in 12 weeks	5	8
Switched over to other treatment in 12 weeks	1	1
At 12 weeks, patients on treatment	70	75
Lost for follow up in 12-24 weeks	7	10
Switched over to another treatment in 12-24 weeks	3	5
Medically indicated hysterectomy	1	3
Patient opted for hysterectomy	2	3
At 24 weeks	60	60
Median age of the women, in years	30.6	31.0
Range in years	24-43	26-45

Table 2

Parameter	At 0 weeks	At 4 weeks	At 8 weeks	At 12 weeks	At 24 weeks
Haemoglobin	7.4, 7.5			9.2,8.6	10.3,10.2
Dysmenorrhoea	43%, 45%			9%, 10%	8%, 14%
ET in mm	11.3, 11.0			5.7, 5.4	5.6,5.9
Range	7.1-15,6.9-14			4.3-10, 4.6-11	4.4-12,4.1-13
Menorrhagia control in % of women		79,46	84,78	82,80	88,76
Mean PBAC score	276,255	109,129	98, 110	86, 92	92,95
Range	125-354, 113-320	74-153, 86-197	70-124, 81-155	76-142, 71-136	80-156, 76-148
Subjective evaluation of amount of bleeding	+++++,+++++	++,++++	++, ++	++,++	++,++
Satisfied about treatment		79,43		70,58	68, 49

Legend: Values in red colour: Group A with Centchroman. Values in black colour: Group b with MPA

The age of the women in group A, median 30.6 years with a range of 24-43 years; where as in group B, the median age is 31.0, with a range of 26-45 years.

The average haemoglobin level in group A women at initiation of treatment was 7.4 Gms%, improved to 9.2 grams at 12 weeks and 10.3 at 24

weeks. The comparative figures for group B were 7.5, 8.6,10.2 respectively

In group A, 45% of women had some dysmenorrhoea at initiation of treatment, and after treatment less than 10% had dysmenorrhoea; compared with 43% at initiation, 8 % at 3 months and 14% at 6 months in group B.

Endometrial thickness was a mean of 11.3mm, with a range of 7.1-15 in group A at initiation of treatment. The mean endometrial thickness was 5.7, 5.4 mm at 12 weeks and 24 weeks. In group

B, the mean endometrial thickness was 11.0, 5.6, 5.9 mm at initiation, 12 weeks and 24 weeks respectively

The mean PBAC scores at initiation of treatment were 276 with a range of 125-354 in group A, and the corresponding figures were 225, 113-320 for group B.

After one month of treatment, 79% of women in group A had control of menorrhoea; in group B only 46% had control of menorrhagia. From two months of treatment, the percentage of women who had control of menorrhagia in group A were 84, 82, 88 at 2,3,6 months respectively; the corresponding values for group B were, 78, 80, 76.

The mean PBAC scores were 109, 98, 86, 92 at 4, 8,12,24 weeks of treatment in group A ; compared with 129, 110, 92, 95 at 4,8,12,24 weeks for group B.

At every visit, the women were asked to assess their bleeding subjectively as per their perception in a scale of 1-5. The median rating of bleeding were 5,4,2,2,2 at 0,1,2,3,6 months in group A; the corresponding ratings in group B were 5,4,2,2,2.

The general assessment of the women, about the treatment—79, 70, 68 % of women were satisfied with the treatment at 1, 2, 6 months of treatment in group A. The corresponding figures for group B were 43,58,49 %.

Discussion

The ultimate aim of the treatment of DUB is control of bleeding and the resultant increase in the haemoglobin level. Both, Centchroman and MPA are useful in the management of DUB.

Ravibabu Komaram et al. noted that the mean PBAC score was reduced by 58% at the end of six months of usage of centchroman⁽⁹⁾

Hari Om Singh et al. reported that there was a reduction of PBAC score from 317 to 105 after six months of usage of centchroman. In this series of patients, at the end of the treatment, 15% of the patients are having heavy or very heavy bleeding⁽¹⁰⁾.

Jacob et al. reported a 74.7% reduction in PBAC score with centchroman and 55.9% reduction with nor ethisterone⁽⁷⁾.

Jimit Kumar Jamana das et al compared centchroman with combined oral contraceptives. In their series of cases after six months of treatment, the PBAC score was reduced by 57% with centchroman and 38% with COC⁽⁸⁾.

Kripalani a et al. in their trend setting study using centchroman, reported that 43% of women had amenorrhoea; 17% had no response; the mean PBAC score was less by 98% after six months of treatment⁽⁵⁾.

Zeepee Godha et al. compared the efficacy of centchroman and MPA in a large series of patients more than 200 in each group. They reported a reduction in median PBAC score by 79.4% in centchroman group and 75% in MPA group⁽¹¹⁾.

In the present study, after a month of usage of centchroman, the median PBAC decreased from 276 to 109 and with MPA from 255 to 129- a reduction of 62.5% vs 49%. While taking into consideration 100 PBAC as the limit of menorrhagia, 79% of women had control of bleeding with centchroman, compared with only 46% in MPA group. But after another cycle of treatment, the MPA group of women had a result almost equal to that of centchroman group of women--78% vs 84%. At completion of six months of usage of both the drugs, the median PBAC came down from 276 to 92 in with centchroman and 255 to 95 with MPA; the overall control of menorrhagia being 88% with centchroman and 76% with MPA. 14 women in centchroman group (23.3 %) and 8 women from MPA group (13.3 %) became amenorrhoeic. The mean Endometrial thickness was 11.3 mm initially and 5.6 mm at completion of treatment with centchroman; and the figures with MPA were 11.0 mm and 5.9 mm.

The results of our study are similar to that quoted by Zeepee Godha et al. In a clinical scenario, it is not the objective PBAC, but the subjective bleeding observed by the patient is important to her. Centchroman patients rated their bleeding as

+++++ at start of treatment and from the first month onwards, they rated the bleeding as ++ till the completion of six months of treatment; whereas women on MPA rated their bleeding as +++++ initially, ++++ at one cycle of treatment, and ++ from two months onwards. The Hb% rose from 7.4 gms % to 10.3 gms% in group A and from 7.5 gms% to 10.2 gms% in group B. Some amount of dysmenorrhoea was complained by 40-45% of women at the start of treatment; and only by 10-15% of women at the completion of treatment. After discontinuation of treatment, the recurrence of the problem was seen in 8 women with centchroman and in 13% with MPA treatment.

Overall, 68% of women in centchroman group and only 49% of women in MPA group are satisfied with their treatment, even though the results are almost same. The reason may be their expectation of a cure of the disease than the management of the problem. Daily usage of MPA. vs once or twice a week usage of centchroman might have weighed in the rating of success from the patient's point of view.

Conclusions

Centchroman is an effective medical management of DUB. More than 3/4ths of women had control of bleeding and 1/4th of women became amenorrhic with treatment. Medroxy Progesterone Acetate is also effective in the management of DUB, but slightly lesser than Centchroman. Both of these drugs are suggested as treatment for DUB, thereby avoiding surgery.

Conflict of interest: Nil

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