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EFFECT OF LOW DOSE MIFEPRISTONE (25 MG) ON LEIOMYOMA- A PROSPECTIVE RANDOMIZED DOUBLE BLIND CLINICAL STUDY

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ABSTRACT

AIM To evaluate the effect of low dose Mifepristone (25mg) on leiomyoma symptoms and uterine leiomyoma in women with symptomatic leiomyomata.

METHODS In this prospective randomized double blind clinical trial 80 women with symptomatic myoma were included. Uterine size >20wks, myoma>15cm were excluded. Variables as baseline uterine size uterine volume, myoma size, volume, hemoglobin, endometrial histology were taken. Patients were randomized and were given drug or placebo for 3 months. Bleeding and pain scores were checked on monthly visits. After 3 months ultrasound and endometrial biopsy were repeated on completion of therapy. Changes in above parameters were tabulated for analysis

RESULTS 80 patients (40 Patients in drug group i.e., group M and 40 patients in placebo group i.e., group C) completed treatment. Menstrual blood loss Index reduced from 150.75+30.14 to 0.00 + 0.0 at the end of 3 months in group M and in Group C there is a slight increase in menstrual blood loss index from 157.5+ 31.77 to 164.00+ 32.02. Mean uterine volume reduced from 212.5206+146.56 to 130.9515 + 96.84 (38.38%) in group M at the end of 3 months and in group c there is a slight increase in uterine volume by 4.91%(187.1148+157.48 to 196.3003 + 157.93) Mean myoma volume reduced by 43.84% in group M where as there is a slight increase in myoma volume by 4.34% in group c at the end of 3 months. Mean hemoglobin level raised from 8.57+ 0.79 to 10.09 + 0.99 in group M. In group c, hemoglobin level drop from 9.44 + 1.11 to 8.78 + 0.93 was observed at the end of 3 months. Repeat endometrial histopathology did not reveal any complex hyperplasia or atypia in either group.)

CONCLUSION Three months treatment of 25mg Mifepristone effectively controls bleeding, reduces the volume of uterus as well as myoma with a rise in hemoglobin status. This avoids blood transfusion and hysterectomy in a lot of symptomatic myoma cases.

KEYWORDS : Myoma, Amenorrhoea, Mifepristone, Medical Management, antiprogesterone.

INTRODUCTION

Uterine leiomyoma are commonest benign gynaecological tumours occurring in up to 25 per cent of women in reproductive age and about 40 per cent have symptoms severe enough to warrant therapy(1). The definitive treatment for symptomatic myomas has always been surgical and myomas account for up to 40 per cent of all hysterectomies in premenopausal women (2).

Non surgical treatment options for symptomatic myomas have limitations. Danazol reduces uterine volume by 18-23 per cent (3) but is associated with marked androgenic side-effects and liver dysfunction. Gonadotrophin releasing hormone agonist (GnRH) reduces Ieiomyoma size to about 50 per cent in three months(4) but is expensive, has to be given parentcrally and is also associated with hypoestrogenism leading to hot flushes, vaginal dryness and bone loss(5). Cessation of GnRH causes regrowth of myoma and recurrence of symptoms (6). Uterine artery embolization has been shown to decrease Ieiomyoma size by 35-69% per cent, improve menorrhagia and reduce pain, but there are potential risks of premature ovarian failure and uterine synechia (7).

Although the traditional concept supports a crucial role of oestrogen in promoting leiomyoma growth, recent evidence suggests that progesterone is essential for maintenance and growth of uterine Ieiomyoma and that oestrogen is required only for upregulation of progesterone receptors(8). Hence, there was a surge of studies evaluating effect of antiprogestogens like ulipristal (PEARL Study), asoprisnil, and CDB-2914, a progesterone receptor modulator, in non surgical treatment of uterine myomas(9,10).

Mifepristone (RU 486) is a progesterone receptor modulator with primarily antagonistic properties. It binds strongly to endometrial progesterone receptors, minimally to estrogen receptors and upregulates androgen receptors (11). In a placebo controlled trial low dose mifepristone (RU 486) has been shown to decrease myoma size as well as symptoms (12). Reduction in **size** with mifepristone might be due to the direct effect in reducing number of progesterone receptors. Besides, because of ovarian acyclicity seen with mifepristone, hormonal milieu similar to early follicular phase may also inhibit steroid dependent growth of myoma. Increase in androgen receptors also contributes to antiproliferative effects (13). Mifepristone also delays or inhibits ovulation, which may produce amenorrhoea. Direct suppressive effects on endometrial vasculature as well as on reducing stromal vascular endothelial growth factor (VEGF) have also been suggested for reducing menstrual blood loss (13, 14).

GnRH analogues are a well established option for medical manageme nt of myomas, but their use is not widespread. Mifepristone, on the other hand, is administered orally, has a few side effects and is less expensive than GnRH analogues. If proved to be an effective medical treatment option for uterine myoma, it may be a cost-effective substitute for GnRH analogues in low-resource settings. The initial studies with mifepristone suggested lesser efficacy with doses <10 mg and also concluded that an effective dose to cause a clinically significant (50%) decrease in leiomyoma volume was 25 mg daily(15). Therefore, this study was designed to evaluate efficacy and safety of low dose (25mg) mifepristone in medical management of uterine leiomyoma.

AIMS AND OBJECTIVES

The aim of the present study is to evaluate the effect of low dose (25 mg) mifepristone on symptoms, size of leiomyoma and hemoglobin level in women with symptomatic leiomyoma

MATERIALS AND METHODS

STUDY DESIGN: prospective randomized double blind placebo controlled clinical trial**.**

SAMPLE SIZE: 80

PROCEDURE:

This prospective randomized double blind clinical trial was conducted at department of obstetrics and gynecology, VIMS Hospital. A total of 80(eighty) women between 20-50 years of age with single or multiple fibroids with symptoms (Menorrhagia, Dysmenorrhea, abdominal lump, dull aching lower abdominal pain, dyspareunia) or the largest fibroid > 5cm on ultrasound were included in this study. Exclusion criteria were : more than 20 weeks gravid uterus size, fibroids > 15cm by ultrasound, sub mucous fibroids, renal or hepatic dysfunction, suspected adenomyosis, current genital infection, endometrial hyperplasia with atypia, hormonal medication with in preceding 3 months, women desiring pregnancy, suspected ovarian, cervical malignancy, hypersensitivity to drug. After a written informed consent, baseline clinical history (including details of menstrual cycle, symptoms and their severity) was noted. Menstrual blood loss was assessed by pictorial blood loss assessment chart scores (PBAC) [16]. A score of 100 or more amounts to menorrhagia. Visual analog scale

(VAS score) was noted for pain. Patients were asked to describe pain on a scale of 0 to 10 before and after treatment with "no pain" at 0 and worst possible pain "at 10". A complete general and gynecological examination was done including some base line blood test (Hemoglobin, Liver and renal function tests). Ultra sound evaluation involved measurement of uterine volume by viscosmi formula:V= 4/3 π W/2 X L/2 X T/2

(W- Uterine width on transverse section through uterine fundus L-Uterine Length on sagittal section from internal os to fundus T-Uterine thickness on sagittal section between anterior and posterial walls) Ultrasound assessment of leiomyoma volume done by formula 4/3 π abc (abc- diameter of sphere in sagittal, coronal and axial dimensions). In case of multiple fibroids, volume of the largest leimyoma was calculated. Endometrium was biopsied in premenstrual phase at the start of the therapy. Mifepristone is available as 200mg tablet. Each tablet was made into 8 equal pieces equivalent to 25mg. Placebo used in this study was calcium tablets which were of equal size that of Mifepristone tablet. Each calcium tablet was also divided into 8 equal pieces. Eighty identical looking packets with 30 pieces of tablets in each packet were made and were numbered from 1-80 by a third party. These packets were randomized to contain either the drug or placebo by the computer generated random numbers by simple randomization techniques. Participants enrolled in the trial were assigned numbers 1-80 and received the drug or placebo accordingly starting from D1-D3 of each cycle. They received the same packet every month for 3 months by a third party. Both patient and investigator were not aware of the drug being dispensed. For data analysis, the packets were decoded at the end of therapy and the participants receiving mifepristone were allotted group M and those receiving placebo were allocated group C. All subjects were followed monthly in premenstrual phase or on a fixed day of each month in case of amenorrhea for 3 months. Patients were enquired for blood loss by PBAC score and leiomyoma related symptoms. Mean blood loss calculated at the end of treatment Hemoglobin liver & renal functions tests were done. Side effects of any were noted. At the end of 3 months ultra sound for uterine and leiomyoma volume and endometrial biopsy were performed.

STATISTICALANALYSIS

Un paired t-test and chi-square test were used to compare the baseline parameters between the drug and placebo groups. Severity of symptoms between and within the groups, the percentage change in various symptoms score and ultra sound parameters at different time points were evaluated by using multiple measures ANOVA. If on comparison by multiple measures ANOVA the difference at different time points was found to be significant the level of significance was determined by using the Tukey's test 5% level of significance P-Value of < 0.05 was taken as significant.

RESULTS:

Total 80 Patients were recruited and followed up for 3 months. (40 from group M is drug group and 40 from group c is placebo group). The results were analyzed and compared. Patients' baseline characteristics were similar in both groups with mean age being 34.60 ± 8.89 and 33.15 ± 8.62 in group M and C respectively. Majority of cases (65%) from both groups were Para 2. Menorrhagia (70-75%) dysmenorrhea (40∈45%) and Pelvic pain (5%) were the symptoms in both groups Post treatment all patients in group M had complete resolution of symptoms whereas in group C symptoms continued to persist. PBAC score after 3 months of treatment reduced from 150.75 ± 30.14 to 0.00 ± 0.0 in group M (% change 100%, P<0.05). All patients in group M had amenorrhea. In group C there is a little increase in PBAC score from 157.5 ± 31.77 to 164.00 ± 32.02. (% change–4.1%, P>0.05). This difference in group M is statistically significant. Only 12 Women in group M had fatigue. No other side effects were noted in both groups.

Uterine volume in group M has decreased after three months Rx whereas in group C there is a small increase in volume. The percentage change in Uterine Volume was -38.38% (P<0.05) and +4.91% (P>0.05) in group M and C respectively (Table I). The increase in mean Uterine Volume might be due to slow growth of Leiomyoma as it was left untreated in group C. Calcium has no effect on growth of uterine leiomyoma. Fibroid Volume has decreased after three months treatment in group M. In group C there is small increase in fibroid volume post treatment. The percentage change in fibroid volume was -43.84% (p<0.05) and +4.34% (P>0.05) in group M and C viz, (Table-II). Hemoglobin level has improved in group M after 3 months of treatment. In group C a decrease in Hemoglobin level was observed. The percentage change in Hb% was +17.74% (P<0.05) and -6.99% (p<0.05) in group M and group C Viz, (Table III).

DISCUSSION

The present study was to evaluate the effect of low dose mifepristone in the management of uterine leiomyomas. In the present double blind randomized placebo controlled clinical trial, 25mg of mifepristone has been used. The drug was started from D1-D3 of cycle that is in the early follicular phase so that it starts acting before the development of dominant follicle.

After treatment for 3months, the effect of drug was evaluated in terms of reduction of uterine volume, volume of leiomyoma and side effects of the drug. In the present study, the mean age was 34.60 ± 8.89 and 33.15 ± 8.62 years is group M and C respectively and similar to the studies of Madhu Bagaria, Amita Suneja et al and Reinschetal [17, 18]. The parity wise distribution of M and C groups was similar to the studies of Madhu Bagaria, Amita Suneja etal and Reinsch etal (65% are para 2). In group M, 20 patients had menorrhagia, 8 had dysmenorrhoea 10 patients had both menorrhagia and dysmenorrhoea. 2 had pelvic pain. In group C, 24 patients had menorrhagia, 12 patients had dysmenorrhoea, 4 had both menorrhagia and dysmenorrhoea. Both groups are comparable in symptomatology. In study conducted by Madhu Bagaria, Amita Suneja etal, Mifeperistone group had 12 patients with menorrhagia 5 had dysmenorrhea and 3 had pelvic pain whereas in placebo group. 11 patients had menorrhagia, 6 had dysmenorrhoea, 4 had both menorrhagia and dysmenorrhoea and 1 had pelvic pain. In the present study amehorrhea was induced in 100% of patients in group M. Symptoms were relieved in 100% of patients in group M during treatment. In group C, symptoms continued during these three months of treatment. In Madhu Bagaria, Amita Suneja etal study amenorrhea was induced in 85% of patients in mifepristone group. Reinsch etal study showed 95% of patients had amenorrhea in mifepristone group. Yen et al study using 25mg of mifepristone showed 100% of patients had amenorrhea. Menstrual blood loss index in the present study was 150.75 ± 30.14 before treatment compared to 0 after treatment in group M. In group C it was 157.5 ± 31.77 before treatment compared to 164 after treatment.

Menstrual blood loss index before and after treatment were comparable with that of Madhu Bagaria et al study. % Change in the mean uterine volume in group M in present study is -38.3%. whereas in Madhu Bagaria, Amita Suneja et al study it was -26.6%. In Reinsch etal study it was -32% change in mean leiomyoma volume in group M in present study is -43.84% where as in Madhu Bagaria, Amita Suneja et al study it was -30.2%

In yen et al study using 25mg of mifepristone, % change in leiomyoma volume is -68.4%. In present study, % change in the hemoglobin in group M is ± 17.74% and in group c it is – 6.99% where as in Madhu Bagaria, Amita Suneja et al study it was +14.5% in Mifepristone group and -2% in control group. In both the groups all patients had normal endometrial histopathology before and after treatment. These results were comparable with that of Reinsch et al study. No cases of endometrial hyperplasia noted in this study. In Madhu Bagaria, Amita Suneja et al study 4.8% of patients in mifepristone group had simple endometrial hyperplasia. All of them showed normal endometrium in histopathology specimens when they underwent surgical intervention. This indicates that the drug induced endometrial changes were reversible. No significant side effects were noted in both the groups only 12 patients in group M had fatigue, though not included in the present study, patients were followed up for 6months after 3 months of treatment. In group M, patients have resumed their menstrual cycle after stopping mifepristone and had no recurrence of symptoms.

CONCLUSION

In conclusion, our results showed that low dose mifepristone therapy (25mg) led to symptomatic relief in myomas, significant reduction of mean uterine volume, significant reduction of mean leimyoma volume, no increased incidence of endometrial hyperplasia and no other side effects.

Endometrial hyperplasia is a notable adverse effect of the drug mifepristone (19). Long term use of high dose of anti progesterone may promote an un opposed estrogen mileu leading to endometrial hyperplasia (20). Although its use as a primary medical therapy is limited due to recurrence after stopping treatment, it can be used as a preoperative adjunct especially in severe anemia, large inoperable fibroids, in premenopausal women to avoid surgery.

TABLE: I

Comparison of mean uterine volume (Mean ± SD, cu.cm) in the two groups before and after treatment (N=80)

	Group M	Group C
Before treatment	212.5206 ± 146.56	187.1148 ± 157.48
After Treatment	130.9515 ± 96.84	196.3003 ± 157.93
% Change	-38.38%	+ 4.91%
P-Value	<0.05	>0.05

TABLE: II

Comparison of mean fibroid volume (Mean + SD, cu.cm) in the two groups before and after treatment (N=80)

	Group M	Group C
Before treatment	139.1529 ± 113.15	170.3764 ± 169.97
After Treatment	78.1486 ± 71.18	177.7757 ± 171.56
% Change	-43.84%	+ 4.34%
P-Value	<0.05	>0.05

TABLE: III

Comparison of mean haemoglobin (Mean + SD, gm%) in two groups before and after treatment

	Group M	Group C
Before treatment	8.57 ± 0.7915	9.44 ± 1.11
After Treatment	10.09± 0.99	8.78 ± 0.93
% Change	17.74%	-6.99%
P-Value	<0.05	<0.05

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