



**ORIGINAL RESEARCH PAPER**

**Gynecology**

**EFFECT OF MIFEPRISTONE IN TREATMENT OF UTERINE MYOMA : AN EXPERIENCE FROM A TERTIARY CARE CENTRE.**

**KEY WORDS:** Fibroid uterus, Mifepristone, PBAC scores, VAS score.

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**ABSTRACT**

**Background:** Uterine leiomyoma are commonest benign gynaecological tumours occurring in up to 25 per cent of women in reproductive age and a common indication for hysterectomy in India. An effective medical treatment option may reduce hysterectomy associated morbidity. The aim of the study was to evaluate effect of Mifepristone (25mg) on uterine fibroid with reference to change in symptomatic profile and reduction in the size of fibroid.

**Methods:** It is a hospital based interventional study conducted in department of obstetrics and gynaecology, at skims soura Srinagar. Eighty women of age 35-50 years having symptomatic myoma meeting inclusion criteria were selected from Gynecology OPD and given 25 mg Mifepristone once daily continuously for three months.

**Results:** Mifepristone treatment significantly reduced mean PBAC score from baseline score of 216.7 to 23.2 at the end of 3rd month of therapy. Mean fibroid volume also reduced significantly from baseline value of 215.8cm<sup>3</sup> to 132.3cm<sup>3</sup> after 3 months of treatment. At the end of therapy hemoglobin was raised from Mean of 8.9g/dl at baseline to 10.2g/dl after 3 months of treatment. No major side effects were observed and 8% (n=10) patients had hysterectomy.

**Conclusions:** Mifepristone is very useful option in women with symptomatic fibroids. It reduces fibroid symptoms and its size without any major side effects. However, long term RCTs are needed to assess the safety and efficacy of Mifepristone.

**INTRODUCTION**

Uterine leiomyoma are commonest benign gynaecological tumor 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). The fibroid prevalence increases with age until the age of menopause and increase in the average age of conception recently is thought to be a contributing factor (30). Fibroids are increasingly resulting in the fertility problems (4).

Non surgical treatment options for symptomatic myomas have limitations. Danazol reduces uterine volume by 18-23 percent, but is associated with marked androgenic side-effects and liver dysfunction(5). Gonadotropin releasing hormone agonist (GnRH<sub>a</sub>) reduces leiomyoma size to about 50 percent in three months(6). But is expensive, has to be given parenterally and is also associated with hypoestrogenism leading to hot flushes, vaginal dryness and bone loss(7). Cessation of GnRH agonists causes regrowth of myomas and recurrence of symptoms (8). Uterine artery embolization has been shown to decrease leiomyoma size by 35-69 per cent, improve menorrhagia and reduce pain, but there are potential risks of premature ovarian failure and uterine synechia (9).

Although the traditional concept supports a crucial role of estrogen in promoting leiomyoma growth, recent evidence suggests that progesterone is essential for maintenance and growth of uterine leiomyoma and that estrogen is required only for upregulation of progesterone receptors (10). 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(11,12).

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 (13). In a placebo controlled trial low dose Mifepristone (RU 486) has been shown to decrease myoma size as well as symptoms (14).

GnRH analogues are a well established option for medical management 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. In recent studies it is proved to be an effective medical treatment option for uterine myoma, and is considered 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).

**MATERIALS AND METHODS**

It is a hospital based prospective interventional study. Permission from institutional ethical committee was obtained. Eighty patients attending the Gynecology OPD at Sher E Kashmir Institute of Medical Sciences, Soura, and Srinagar with symptomatic fibroids fulfilling the inclusion criteria were selected between Jan 2016- Jan 2018. Written informed consent was taken from patient. Relevant history was taken. A complete general and gynaecological examination was done. Blood samples were collected for checking Hemoglobin (g %), liver function tests and kidney function tests. Ultrasound (USG) was done. Endometrial aspiration was performed to rule out any abnormal histopathology in patients as indicated. Patients with inclusion criteria were given, Tab Mifepristone 25mg daily for 3 months. Patients were followed up at 1 month after starting treatment and at 3rd month. On each visit clinical symptoms were assessed i.e. heavy menstrual bleeding by PBAC (Pictorial Blood Assessment Chart) score and pain related symptoms by VAS (Visual analogue score). Side effects experienced were also noted. Pictorial blood loss assessment chart (PBAC) score, is a semi quantitative method for assessment of menstrual blood loss and it takes into account the number of pads soaked, degree of soakage, passage of clots and episodes of flooding(16,17). A score of 100 or more indicate menorrhagia. For pain assessment Visual analogue score (VAS) was used. Dysmenorrhoea, abdominal pain, dyspareunia, and backache were assessed using VAS score. Patients were asked to describe their pain severity both before and after the treatment on a scale of 0 to 10. When there is "no pain" taken at zero and for "worst possible pain" at ten. USG was done to assess the number, type, volume of fibroids and to rule out other pelvic pathology.

Volume of fibroid was calculated by Ellipsoid method and the formula  $V=0.5233 (D1 \times D2 \times D3)$  was used, where D1, D2 and D3 are the longitudinal, transverse and cross sectional diameters of the fibroid, respectively. In multiple fibroids each fibroid volume is added to calculate total fibroid volume.

**Inclusion Criteria**

- Women between 35-50 years of age
- Symptomatic patients of fibroid uterus.
- Fibroid size less than 15 cm on USG.

**Exclusion Criteria**

- Fibroids size more than 15 cm on USG.
- Clinically fibroid is more than 20-week size of gravid uterus.
- Hepatic or renal dysfunction.
- Hormonal contraception or medication received (Progestogens/GnRH<sub>a</sub>) in the last 3 months.
- Current genital infection.

**Statistical Analysis:**

continuous variables were expressed as Mean±SD and categorical variables were summarized as frequencies and percentages. A P-value of less than 0.05 was considered significant.

**RESULTS**

As shown in Table 1 Age range of patients in present study was from 35 to 50 years. In present study 55% of patients were in age group of 41 to 45 years and 25% of patients were in age group of 35 to 40 years, 20% of patients were in the age group of 46 to 50 year

**Table 1: Age wise distribution of fibroid uterus cases.**

Age(years)	Number(n)	Percentage(%)
35-40	20	25%
41-45	44	55%
46-50	16	20%
Total	80	100%

Table 2 depicts the distribution of body mass index (BMI) in the study population. In the present study mean body mass index was 26 Kg/m<sup>2</sup> and range was from 18 to 38 Kg/m<sup>2</sup>. Most of patients (55%) in this study were in normal range of BMI (18-25) and 45 % of patients had high BMI (>25). Obesity is associated with hyper estrogenic state contributing to myoma growth.

**Table 2: Distribution of BMI in the study group.**

BMI(kg/m <sup>2</sup> )	Number(n)	Percentage (%)
18-25	44	55%
25.01-30	24	30%
30.01-35	10	12.5%
35.01-40	2	2.5%

Table 3 shows the distribution of symptoms with which fibroid patients presented. In the present study heavy menstrual bleeding (87.5%) in the form of menorrhagia or polymenorrhoea was common symptom followed by pain related symptoms (75%) which includes dysmenorrhoea, backache and abdominal pain. Mass per abdomen was complained by only 6.25% patients in the present study. Most of (80%) patients had above depicted symptoms for more than 6 months of duration.

**Table 3: Distribution of symptoms in the study group.**

Symptoms	Number(n)	Percentage (%)
Heavy menstrual bleeding	70	87.5%
Pain	60	75%
Mass per abdomen	5	6.25%

Table 4 depicts distribution of different types of fibroids in study population. In the present study sub mucosal fibroids (55%) are the most common type of fibroids, as only

symptomatic fibroid patients were recruited this study followed by intramural type (40%) and rare variety was sub serosal type (5%). 85% of patients had single fibroid as per ultrasound (USG) report and only 15% cases had multiple fibroids.

**Table 4: Distribution of types of fibroids in study group.**

Fibroid type	Number(n)	Percentage (%)
Sub mucosal	44	55%
Intra mural	32	40%
Sub Serosal	4	5%
Total	80	100%

Table 5 shows the effect of Mifepristone in reducing blood loss which was assessed using pictorial blood loss assessment chart (PBAC) score. Baseline mean PBAC score was 216.7. At 1 month of follow up, majority of patients stopped bleeding so the mean PBAC score was reduced to 42.9, which is statistically significant. At 3rd month of follow up most patients continued to have amenorrhoea and only few patients had per vaginal spotting and the mean PBAC score was 23.2, which again showed statistically significant reduction in mean blood loss.

**Table 5: Effect of Mifepristone on pictorial blood loss assessment chart (PBAC) score.**

Time Period	Mean	SD	Range	Difference from BL	P value*
Baseline(BL)	216.7	63.84	72-291	-	-
1 month	42.9	28.91	19-192	173.8	<0.001
3 month	23.2	24.17	13-158	193.5	<0.001

In the present study effect of Mifepristone in reducing pain was assessed using visual analog scale (VAS) score and it is shown in Table 6. Baseline mean VAS score for pain related symptoms was 5.17 before starting Mifepristone therapy. At 3rd month of follow up there was statistically significant reduction in mean VAS score to 2.45 indicating improvement in patient quality of life.

**Table 6: Effect of Mifepristone on visual analog scale (VAS) score.**

Time Period	Mean	SD	Range	Difference from BL	P value
Baseline(BL)	5.17	2.91	1-8	-	
Three months	2.45	1.87	0-6	2.72	<0.001*

Table 7 depicts the effect of Mifepristone in reducing the fibroid volume. In the present study the mean fibroid volume was 215.8 cm<sup>3</sup> before starting treatment and after completing 3 months of treatment mean fibroid volume was reduced to 132.3 cm<sup>3</sup> which is statistically significant. Overall 38.7% reduction in fibroid volume is observed in this study.

**Table 7: Effect of Mifepristone on fibroid volume.**

Time Period	Mean	SD	Range	Difference from BL	P value
Baseline (BL)	215.8	918.7	3.7-6582	-	
Three months	132.3	143.2	0-378	83.50	<0.001*

**Table 8: Effect of Mifepristone treatment on haemoglobin.**

Characters	Baseline	At 3 months	P - value
Haemoglobin (g%) (Mean±SD)	8.9±1.74	10.2±2.08	0.008 <sup>†</sup>

Table 8 shows the effect of Mifepristone in improving the Haemoglobin level in the fibroid patients. In the present study the baseline Haemoglobin (g %) was 8.9±1.74gms/dl i.e. before starting treatment. After 3 months of treatment there was statistically significant rise in Hb% to 10.2±2.08gms/dl. Mifepristone reduces the blood loss thereby improving the Haemoglobin level so is more useful in anaemic patients.

Majority of patients had no side effects (n=68, 85%). Only

minor side effects were observed in few patients i.e. joint pain (n=5, 6.25%), hot flushes (n=3, 3.75%) and headache (n=2, 2.5%). At 3rd month of follow up there was raise in liver enzymes (ALT,AST) in 3.75% (n=3) of patients and on subsequent follow up liver enzymes returned to normal level within 4 months without any intervention. In the present study 8% (n=10) of patients underwent hysterectomy during study period, as they continued to have heavy menstrual bleeding and pain related symptoms.

**DISCUSSION**

Uterine fibroids are the most common benign tumours of uterus and are the most common indication for hysterectomy. As there is no single agent that could be used as a definitive treatment for fibroid uterus, and wide range of options are available for management of fibroid based on the patient's clinical profile. Gonadotropin releasing hormone agonist, Danazol, gestrinone, selective estrogen receptor modulators (SERMs), aromatase inhibitors, cabergoline, antiprogesterins (RU486 and asnoprisinil) are potential drugs available for treatment of fibroid uterus.

Mifepristone, as a treatment option for myoma, was first reported by Murphy et al in 1993(18). Further studies evaluated Mifepristone in doses varying from 2.5 to 50 mg/day given for 3 to 6 months and doses as high as 50 mg and as low as 5 mg were found effective in ameliorating myoma related symptoms like dysmenorrhea, menorrhagia and pelvic pressure, and reducing myoma volume by 26-57 per cent and inducing amenorrhea in 41-100 percent (15, 19-26). Ultra low dose of 2.5 mg also resulted in appreciable symptomatic relief, modest 11 per cent reduction in uterine volume suggesting a possible dose effect with improvement in quality of life (27).

In the present study heavy menstrual bleeding(87.5%) and pain related symptoms (75%) were main problem for women, compelling them to visit health care facilities, as it was affected their day to day activities. Similarly, in study conducted by Brig Vinod Raghav et al, common presenting complaints were menorrhagia (86%), abdominal pain (28%), dysmenorrhea (18%), dyspareunia (8%)(28). In the present study baseline, 1 month and 3-month PBAC score was 216.7, 42.9, and 23.2 respectively. Comparable results are reported by Kulshrestha et al i.e. baseline, 1 month and 3 month, PBAC score of 289.2, 44.9, and 19.8 respectively in patients who were given 25mg of Mifepristone daily(29). And during treatment period, most (90%) patients had amenorrhea like in all other studies.

In the present study there was statistically significant improvement in hemoglobin level after completing treatment. Comparable results were reported by Shikha Seth et al and Kulshrestha et al(29,30). In present study percentage of fibroid volume reduction noted was 38.7% similarly in study conducted by Kulshrestha et al and by Nachiketha SV et al where there was 36% and 38% reduction with 25 mg and 50mg of Mifepristone respectively(29,31).Hysterectomy was done in 8% of patients, in whom heavy menstrual bleeding continued despite of Mifepristone treatment. Shikha Seth et al also reported that 12.1% of their patients had hysterectomies due to recurrence of symptoms like menorrhagia and increase in fibroid volume, similarly 7% of patients had hysterectomies in a study by Nachiketha SV et al (30,31).

**CONCLUSION**

Mifepristone is very useful option in women with symptomatic fibroid and it can also be used as a preoperative adjunct in patients with severe anemia and large fibroid when surgery is anticipated to be difficult. It reduces fibroid size and its symptoms without any major side effects. However, future long term RCTs are needed to assess the safety and efficacy of Mifepristone.

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