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Original Research Article

Efficacy of mifepristone in the management of fibroid

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ABSTRACT

Background: Uterine fibroids are the most common benign tumors of the uterus. The incidence has been shown to be as high as 70–80 percent in studies using histologic and sonographic examinations. Majority of fibroids are asymptomatic and when symptomatic, patients present with menstrual disturbances, infertility, lump abdomen or pressure effects. The complications associated are severe anemia, hyaline or red degeneration, urinary retention, hydronephrosis secondary to obstructive uropathy and rarely sarcomatous changes. The treatment depends upon the size, symptoms, location and age of the patient. The aim and objective of this study is to evaluate the effectiveness of Mifepristone in symptomatic improvement and reduction of the size of fibroid.
Methods: The study was conducted in Sri Venkateswaraa Medical College Hospital and Research Centre (SVMCH and RC), Puducherry. This is a hospital based longitudinal study conducted in between December 2019 to June 2021 for a period of 18 months. 30 consecutive cases were studied based on inclusion criteria. All patients were treated with mifepristone 50 mg once weekly for 6 months. Analysis was performed by using statistical package for the social sciences (SPSS) version 23 software.
Results: In this study we observed there was a significant improvement in the hemoglobin (Hb) level, significant reduction in uterine volume, fibroid size and endometrial thickness after 6th month follow-up.
Conclusions: Mifepristone was able to significantly improve the patient outcome by reducing the amount of blood flow during menstruation and increasing the Hb levels and significantly reduce the size of myoma.

Keywords: Mifepristone, Uterine fibroids, Myoma

INTRODUCTION

Uterine fibroids are the most common benign tumors of the uterus. The incidence has been shown to be as high as 70–80 percent in studies using histologic and sonographic examinations. Majority of fibroids are asymptomatic and when symptomatic, patients present with menstrual disturbances, infertility, lump abdomen or pressure effects. The exact etiology of fibroids is debatable but many factors are reported to have some role in the pathogenesis of fibroids including genetic, hormonal and biological factors. The risk factors for developing fibroids include obesity, nulliparity, younger age at menarche and African race.

The complications associated with uterine fibroids may include severe anemia, hyaline or red degeneration, urinary retention, hydronephrosis secondary to obstructive uropathy and rarely sarcomatous changes.[1,2] The treatment of uterine fibroids depends upon the size, symptoms, location and age of the patient.

In patients having severe symptoms affecting quality of life considerable surgical management may be required. Minimally invasive surgeries like hysteroscopic myomectomy (for submucosal fibroids), laparoscopic myomectomy (for symptomatic subserosal and less commonly for intramural fibroids), abdominal myomectomy and hysterectomy (when woman no longer wishes to preserve uterus or fertility like in

perimenopausal women or in women where sarcomatous changes are suspected on imaging.[3] Other less invasive procedure include uterine artery embolization and magnetic resonance guided focused ultrasound surgery (MRgFUS).[4]

Medical treatment is given to relieve the symptoms like heavy menstrual bleeding and pain so as to improve the overall quality of life. Drugs available are antifibrinolytics – e.g. tranexamic acid, danazol, GnRH analogs, progestogens and the antiprogesterone – e.g. mifepristone.

The progesterone controls the growth of fibroid and causes proliferating cell nuclear antigen (PCNA) and EGF expression and upregulation of fibroid cells and increases the expression of Bcl-2 protein, which is apoptosis-inhibiting gene product of the oncogene Bcl-2. Progesterone decreases the expression of tumour necrosis factor α (TNFα), this is important cytokine involved in apoptosis. There is significant reduction in the overall mitotic activity and volume of fibroids if antiprogesterone drug i.e. mifepristone (RU 486) is given.[5]

Mifepristone is a progesterone receptor modulator with primarily antagonistic properties, and it has antiglucocorticoid action also. Mifepristone has direct effect in reducing number of progesterone receptors which contributes to the reduction in size of fibroid. It causes ovarian acyclicity and results in hormonal milieu similar to early follicular phase that may inhibit steroid dependent growth of fibroid. It also causes inhibition of ovulation resulting in amenorrhea.

Reduction in stromal vascular endothelial growth factor (VEGF) and direct suppressive effects on endometrial vasculature by mifepristone have been suggested in decreasing the menstrual blood loss.[6]

The aim and objective of this study is to evaluate the effectiveness of mifepristone in symptomatic improvement and reduction of the size of fibroid.

METHODS

This hospital based longitudinal study was conducted in the department of obstetrics and gynecology at Sri Venkateshwaraa Medical College Hospital and Research Institute (SVMCH and RC), Ariyur, Puducherry, in between December 2019 to June 2021 for a period of 18 months. 30 consecutive cases were studied based on inclusion criteria. All patients were treated with mifepristone 50 mg once weekly for 6 months. Analysis was performed by using statistical package for the social sciences (SPSS) version 23 software.

Sample size calculation

30 consecutive cases were included with confidence interval of (95%) and acceptable margin of error (5%)**.** Sample size was calculated by using (Open Epi software).

Inclusion criteria

Perimenopausal age group – (40-52 years), with symptomatic fibroids of size of more than 2 cm, parous women who have completed family and those who gave consent for the study and women who were agreeing to have an ultrasonography (USG) and endometrial sampling before starting the treatment and after the completion of treatment.

Exclusion criteria

Women who took hormonal contraceptives and who have not completed family and infertile women. Women who have received hormonal therapy in the last 3 months, women having any contraindications for receiving antiprogesterones, active liver disease, severe respiratory disease, renal disease, coagulation defect, and thromboembolic disease and who refused to give consent for the study.

Methodology

Study participants with fibroid was included in the study as per selection criteria. The purpose, procedure and benefits of the study was explained in detail to the participants and then written consent was obtained in their own language. Baseline investigations was done for all the participants which includes haemoglobin (Hb), total count (TC), differential count (DC), erythrocyte sedimentation rate (ESR), bleeding time (BT), computed tomography (CT), renal function test (RFT), liver function test (LFT), and peripheral smear. Endometrial sampling was done premenstrually to study the histopathology of the endometrium and USG will be done to accurately document the volume/size of fibroid, number of fibroid(s), location of fibroid and to measure the endometrial thickness. Patients was asked to take mifepristone 50 mg once a week on a fixed day for 6 months. Patients was reviewed at the end of 1st, 4th and 6th month of the study. In case of any adverse drug reactions participants were asked to stop the drug immediately and report to the emergency unit or OBG OPD. Patients with complaints of amenorrhea in the course of the study were assessed to rule out pregnancy.

USG was done at the end of 6 months after the completion of treatment to assess the fibroid volume, regression in the size of fibroid and to assess the endometrial thickness. Repeat endometrial sampling should be done at the end of 6 months to rule out drug induced endometrial hyperplasia.

Statistical analysis

All data was entered in a Microsoft excel sheet and statistical analysis was done by SPSS version 23.0. Descriptive statistics and paired t test was used to analyse the data. When p value is <0.05 – it was considered significant.

Ethical consideration

Confidentiality of all the patients was maintained. Informed consent was taken from all the patients. The permission to conduct the study was obtained from institutional ethics committee and research committee.

RESULTS

The study was conducted in the department of obstetrics and gynecology at SVMCH and RC, Ariyur, Puducherry. A total of 30 peri-menopausal women, age group of 40-52 were included in this study. In this study most of the women were in the age group of 40-45 (60%) followed by 46-50 (33%) and >50 (7%) (Table 1). Regarding parity details most of the women were parity-II (93%) (Table 2).

Table 1: Distribution of study group based on age.

Age group	Frequency	%
40-45	18	60
46-50	10	33
>50	2	7
Total	30	100

Table 2: Distribution of study group based on history of parity.

Parity	Frequency	%
I	1	3.5
II	28	93
III	1	3.5
Total	30	100

In this study one women had history DM under medication for 10 years and 1 patient had HTN under medication for 15 years and 28 of them had no comorbidity. Regarding complaints most of the women had complaints of HMB and dysmenorrhea (Table 3).

Table 3: Distribution of study group based on complaints.

Complaints	Frequency	%
Dysmenorrhea	8	27
HMB	7	23
Dymenorrhea, backache	1	3
HMB, backache	2	7
HMB, dysmenorrhea, backache	1	3
HMB, dysmenorrhea	11	37
Total	30	100

In this study we observed there was a significant improvement in the Hb level after 6th month follow-up ($p \leq 0.0001$) (Figure 1). In this study the uterus volume was significantly reduced at 6th month of treatment. One patient was not responded to the treatment which showed increased uterus volume by 35.5 cm ($p \leq 0.0001$). Fibroid size reduced significantly 6th month follow up of post treatment ($p=0.0133$). ET was reduced significantly at 6th month post treatment follow-up ($p<0.0001$). Regarding complaints all the women had amenorrhea during the treatment period.

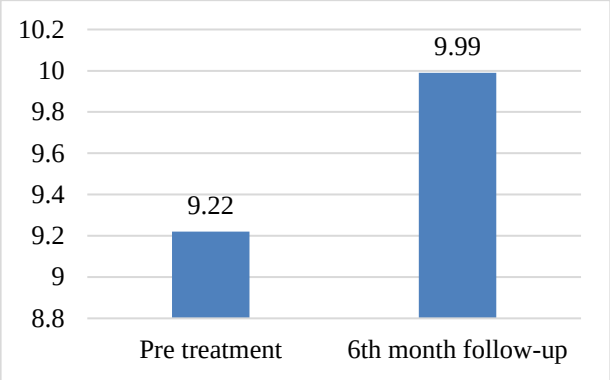

Figure 1: Distribution of pre and post treatment Hb level.

Table 4: Distribution of pre and post treatment fibroid size.

Variables	Pre treatment	6th month follow-up
Minimum	4.000	2.240
Maximum	42.24	34.80
Mean	13.71	9.182
Standard deviation	8.436	6.994
Lower 95% CI	11.05	6.945
Upper 95% CI	16.37	11.42
Total	30	100
P value	0.0133	
R squared	0.1470	
Mean of differences	4.547	
SD of differences	11.09	
95% confidence interval	0.9997 to 8.094	

Table 5: Distribution of pre and post treatment uterus volume.

Variables	Pre treatment	6th month follow-up	6th month follow-up- pre treatment
Minimum	45.26	24.76	-35.15
Maximum	449.8	309.2	167.0
Mean	188.9	121.0	67.92
Standard deviation	102.6	66.80	45.28
Lower 95% CI	150.6	96.07	51.01
Upper 95% CI	227.2	146.0	84.83
P value	<0.0001		
R squared	0.6995		

Table 6: Distribution of pre and post treatment endometrial thickness.

Variables	Pre treatment	6th month follow-up	6th month follow-up- pre treatment
Minimum	2.700	2.500	0.2000
Maximum	12.00	10.60	2.000
Mean	7.018	6.043	0.9750
Std. Deviation	2.339	2.040	0.4766
Lower 95% CI	6.111	5.252	0.7902
Upper 95% CI	7.925	6.834	1.160
P value	<0.0001		
R squared	0.8127		

DISCUSSION

Uterine myomas (fibroids) are the most common benign tumours found in up to 70% women during their reproductive years.[7] Hysterectomies for leiomyoma constitute a third of all hysterectomies. Thus, healthcare cost to society due to uterine leiomyomas is of considerable importance. The treatment of uterine myomas ranges from hysterectomy to medical therapy. However, research is still on for the optimal management option for uterine leiomyoma. Amongst the wide spectrum of drugs available for the medical treatment of myomas, mifepristone may just prove to be the drug of choice in future. The present study is an endeavour towards the exploration of this approach for the management of uterine myoma. The average age of recruitment in our study population was 40-45 years which is similar to other studies in literature thereby suggesting that a large number of premenopausal women are in need for treatment of symptomatic leiomyomas.[8]

Most of the patients included in the study were in II parity (93%) followed by III parity (3.5%) and I parity (3.5%). Similarly Shaikh et al reported that most of the women in both the mifepristone 25 mg and mifepristone 50 mg groups were in para 2 (31 versus 24 patients) followed by para 3 (12 versus 15 patients). Singh et al also reported that maximum number of cases in their study were para 2 and married.[9,10]

In our study one woman had history of DM under medication for 10 years and 1 patient had HTN under medication for 15 years and 28 of them had no comorbidity. Similarly Charles et al recorded co-morbid medical conditions include: obesity, 22.54%; anemia, 20.92%; transfusion-dependent anemia, 3.26%; hypertension, 14.95%; psychiatric disorder, 8.97%; hypercholesterolemia, 7.33%; hypothyroid, 5.43%; uterine polyps, 3.53%; diabetes mellitus, 2.99%; endometriosis, 2.17%.[12]

Our study reported the mean height of women was 154.4 cm, the mean weight was 58.9 kg and the mean BMI was 24.01. Similar to our study Das et al revealed that there is significant increase of BMI value ($p<0.05$) (BMI=26.00±2.98) among those suffering from UF more than 10 months. Weight (63.19±7.39) is significantly higher and obesity also found among woman suffering for more than 10 months. There was increased rate of hypertension among those suffering from UF more than 10 months than those who have developed UF for less than 10 months. Weight is significantly higher among those suffering from UF for more than 10 months.

In this study most of the women had complaints of heavy menstrual bleeding (HMB) and dysmenorrhea, similarly Arora et al reported that all 120 patients in his study reported with HMB as the primary symptom, the severity of which was scored as per the PBAC scoring system.[13] It was observed that with mifepristone all patients without exception had amenorrhoea bringing this score to 'zero'. Also Singh et al reported that most common complaint were HMB with (86% versus 82%), dysmenorrhea (40% versus 44%), dyspareunia (10% versus 12%), pelvic pain/pelvic mass (36% versus 42%), back pain (20% versus 18%). Prasad et al in his study found HMB 60% and dysmenorrhoea 40% at the start of the treatment.[10]

In this study 63% of the women were seen with single fibroid lesion and 37% were observed with two lesion. About 27 women were observed with intramural type and 3 of them observed with both intramural and sub mucosal type lesion. Sathyanarayanan et al evaluated the efficacy of mifepristone in the management of fibroids among 60 women where he reported single fibroid in 31 women, two fibroid in 23 women, three or more fibroids were seen in 6 women.[14] The study also reported that about 54 (56.8%) patients reported with intramural fibroid type, 32 (33.7%) patients reported with submucosal fibroid type, and 9 (9.5%) patients with subserosal fibroid type. Arora et al reported that about 63% of patients were having intramural fibroids, 33% had submucosal fibroids and 3% had subserosal fibroids.[13]

Our study reported that there was a significant improvement in the hemoglobin level after 6th month follow-up ($p\leq0.0001$). Similarly Sathyanarayanan et al reported that haemoglobin rose from 8.86 gm% to 10.88 gm% after three months of treatment and iron supplementation.[14] Singh et al reported the mean levels of haemoglobin from 9.346 in ulipristal acetate group and 9.508 in mifepristone group before the therapy to 10.186 and 10.164 respectively after 3 months of therapy, but the rise in levels was insignificant.[10]

In 1998 Englund et al first described use of mifepristone for the treatment of uterine fibroid. They showed uterine fibroids to be steroid hormone dependent tumors possessing estrogen and progesterone receptors (ER and PR).[15] They proposed that antiprogesterone reduce the size of uterine fibroids either by blocking the effect of

progesterone or interference of estrogen action on fibroids. Baseline ultrasound examinations were obtained and repeated monthly during treatment as a measure of fibroid size. The authors found that fibroid volume (mean±SE) decreased 21.9±4.8% after 4 weeks, 39.5±6.6% ($p<0.001$) after 8 weeks and 49.0±9.2% after 12 weeks of treatment compared to pre-treatment measurements. They further found that administration of mifepristone was associated with a significantly reduced immune-reactivity in fibroids as compared with tissues from untreated patients, this suggested that mifepristone caused regression of fibroids through a direct antiprogesterone effect.

Similarly our study reported that the uterus volume was significantly reduced at 6th month of post treatment and also reported the mean reduction in fibroid volume at the end of the treatment. The fibroid size reduced significantly at 6th month follow up of post treatment ($p=0.0133$). One patient did not respond to the treatment which showed increased uterus volume by 35.5 cm ($p\leq0.0001$). Also Singh et al reported a significant reduction in the fibroid volume at the end of treatment among ulipristal acetate group and mifepristone group. Mean value of the volume of fibroid was taken in both the groups in terms of (cm^3). The mean fibroid volume at the start of the treatment in ulipristal acetate group and mifepristone group were 35.41 and 34.85 respectively and at the end of 3 months were 27.85 and 23.95 respectively. Thus the mean reduction in myoma volume was found to be significant. Although, mifepristone was able to significantly reduce the fibroid volume to 31.2% as compared to 21.34% reduction seen by ulipristal acetate. Even though the size of the myoma had increased after 3 months post treatment follow up (i.e.) 31.24 in ulipristal acetate group and 27.59 in mifepristone group but not to the initial value.[10]

Arora et al reported that, the mean fibroid area at the beginning of the study was 8.95 cm^2. After 6 months of taking tablet mifepristone, significant reduction in all dimensions of fibroid leading to an overall reduction in area was observed ($p=0.001$).[13] The mean area after 6 months treatment was found to be 5.65 cm^2. It was also observed that after 6 months of treatment with tablet mifepristone the mean percentage reduction in the size of fibroid in the study population with intramural fibroid was 36.99% and that with submucosal fibroid was 39.39%. This percentage of size reduction was found to be significant when compared with control group. Similar findings were published in F1000Medical reports in 2009 by Kirsty et al where with the dose of 5 mg or 10 mg mifepristone for 6 months, size reduction of 50% was observed.[16]

In our study ET was reduced significantly at 6th month post treatment follow-up ($p<0.0001$). Regarding complaints all the women had amenorrhea during the treatment period. Arora et al reported that, after 6 months of treatment with mifepristone the average endometrial thickness was 7.34 mm.[13] Moreover, not much difference in endometrial thickness was observed in the test and the control groups as the mean endometrial thickness was found to be 7.34 mm and 6.27 mm respectively. Mifepristone, an anti-progesterone, leads to amenorrhoea after 2nd/3rd dose of 50 mg biweekly in all patients without exception. Moreover, it was concluded that after completion of the treatment course, the patients resumed their menstrual cycle in an overall average time of 1.93 months (1.95 months in the intramural sub-group and 1.89 months in the sub-mucosal sub-group).

CONCLUSION

We conclude that uterine myoma is a common pathology which usually presents with Heavy menstrual bleeding, dysmenorrhea, pelvic pain, dyspareunia or back pain in gynaecology OPD, with majority of them responding to medical therapy. On evaluating the management of mifepristone, it was found that mifepristone was able to significantly improve the patient outcome by reducing the amount of blood flow during menstruation and increasing the haemoglobin levels. Mifepristone was able to bring symptomatic relief in the patients and were able to significantly reduce the size of myoma also the drug showed reversible proliferative endometrial changes. Hence our study reported that mifepristone was found to be better drug in medical management of myoma however larger study population with prolonged or multiple treatment cycles are suggested for better comparison.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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