

A Prospective Study on Effect of Low Dose Mifepristone in Uterine Leiomyoma

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Abstract

Context: Uterine leiomyomas is the most common benign tumor of the uterus and one of the most frequent indications for operative procedures. High dose of mifepristone used to treat leiomyomas have resulted in side effects. Hence this study was done to evaluate effects of low dose mifepristone.

Aims: To evaluate the effectiveness of low dose Mifepristone in the treatment of Uterine Leiomyoma.

Settings and Design: A prospective observational study was conducted among 60 women diagnosed with uterine leiomyoma in a tertiary hospital at Karaikal.

Methods and Material: Data was collected using standardized questionnaire. Blood investigation and ultrasound pelvis was done to evaluate the effects on uterine leiomyoma before and after treatment with 10 mg of mifepristone for three months.

Statistical analysis used: Mean and standard deviations were used to present quantitative data. Association was tested using Chi square, McNemar test, Paired t test and Wilcoxon test.

Results: Maximum participants were between 40-49 years. More than half of the study participants were relieved of dysmenorrhea after the treatment. The Mean PBAC values reduced from 124.6 ± 51.85 to 34.72 ± 17.87 which was highly significant. There was significant reduction in the uterine volume from 331.69

± 216.05 to 239.68 ± 157.23 cm³ and the Leiomyoma volume from 68.62 ± 38.94 to 46.71 ± 27.96 cm³. About 78% of the study population experienced amenorrhea after the therapy.

Conclusions: Low dose of Mifepristone was effective in reducing the size of uterine leiomyoma and also decreasing symptoms of dysmenorrhoea and menorrhagia thus improving the general health status and quality of life of the study population.

Keywords: Amenorrhea; Dysmenorrhea; Leiomyomas; Mifepristone.

Introduction

The most common benign tumor of uterus is leiomyoma which constitutes 20-40% of all the tumors affecting women in reproductive age. The leiomyomas are symptomatic in 20-50% of all cases where as many women are asymptomatic. Clinical symptoms are usually excessive or irregular menstrual bleeding, problems resulting from adjacent organs pressure, sterility miscarriage or problems during the labour [1]. It is one of the most frequent indications for operative procedures in woman of reproductive age which is associated morbidity, mortality and huge economic burden.

Major contributor for uterine leiomyoma is usually estrogen and the fibroid growth is promoted by progesterone by promoting fibroid cell mitosis. An antiestrogen hormone Mifepristone antagonizes progesterone at receptor levels and many clinical studies suggested that treatment with Mifepristone for leiomyoma can improve the symptoms and reduces the size of uterine fibroids. This makes the surgery simple and also avoids other organ injury, reduces the procedure time, minimizes bleeding, so that the recovery of the patient will be faster [2].

Many studies were done with higher doses of mifepristone for leiomyoma which resulted in higher side effects like fever, giddiness, GI disturbances and breathing difficulties [3,4]. Our study aims to prove low dose of Mifepristone for 3 months is effective in reducing the problems of leiomyoma and the side effects of higher doses of Mifepristone.

Subjects and Methods

A prospective observational study was conducted in the Department of Obstetrics and Gynaecology in Vinayaka Mission's Medical College and Hospital, Karaikal during a period of 12 months from October 2016 to September 2017 after obtaining the approval from the Institutional Ethical Committee.

Our sampling frame consisted of patients who were diagnosed with Fibroid Uterus in the department of Obstetrics and Gynaecology. After obtaining informed and written consent in understandable language from the patients diagnosed with uterine leiomyoma, the following inclusion and exclusion criteria were seen.

Inclusion Criteria

- Females over 35 years.
- Uterine leiomyoma corresponding to less than 12 weeks of size.
- Presence of Menstrual complaints like dysmenorrhoea, menorrhagia.

Exclusion Criteria

- Pregnant and lactating women.
- Known case of ovarian, cervical or uterine malignancy.
- Any history suggestive of hormonal treatment in the past three months.

- Uterine leiomyoma corresponding to more than 12 weeks of size.
- Patients with co-morbid conditions like Diabetes, Hypertension and Dyslipidemia.
- Patients who were not willing for medical management.

Out of 81 cases who were diagnosed with leiomyoma during the study period, 21 cases were excluded as per the exclusion criteria given above. This study includes 60 cases of leiomyoma received tablet Mifepristone 10 mg once daily for 3 months.

Socio demographic details were collected using standardized questionnaire by interview method. Basic blood investigations like Hemoglobin estimation, Liver function test and Urine analysis were done. Ultrasound evaluation of pelvis involving measurement of uterine volume and leiomyoma volume was carried out.

Viscosmi formula was used for the calculation of uterine volume, that is, $\frac{4}{3} \pi W/2 \times L/2 \times T/2$, Where W- width of uterus, L- longitudinal diameter, T- transverse diameter.

Assessment of leiomyoma volume was done by the formula $0.5 \times abc$, where abc represent radii of the sphere in three dimension.

Tablet Mifipristone 10 mg was started as an outpatient department basis as once daily from the second day of cycle for 3 months. Patients were asked to review on every 2nd day of each cycle for the assessment of symptoms and for the issuing of tablets. If the patient has not established cycle, she can visit OPD as the same date of last month.

At the end of 3 months, the subjective evaluation was done by the presence of Dysmenorrhoea elicited by history about the current menstrual cycle. The objective evaluation was done using Pictorial Blood Assessment chart (PBAC) and Ultrasound for reassessment of Uterine and leiomyoma size.

Data was entered in Microsoft excel sheet and analyzed using SPSS 16 software. The Pre-test, Post test, Mean and Standard deviation were done using paired t test and Wilcoxon test. Pre-test and Post test proportions were done using chi square test and McNemar test. p value of less than 0.05 was considered to be significant.

Results

Sixty patients were included in the study and the results were analyzed. More than two third of the study population was between 40 to 49 years

and least was in 35 to 39 years age group (Figure 1). Half of the fibroid cases were Intramural type (51.6%) followed by Sub mucosal (38.9%) and least were Subserosal type (9.5%). Out of sixty, half of them were presented with one fibroid while six of them had three fibroids (Figure 2).

In the present study for the subjective evaluation after giving Mifepristone, study population was asked about symptoms of Dysmenorrhoea. More than half of the study population were relieved of dysmenorrhoea after taking Mifepristone. The difference between pre and post test was highly significant (Table 1).

The objective evaluation for effectiveness of Mifepristone was done using PBAC, Uterine and Leiomyoma Volumes at the end of 3 months. The Mean score of PBAC before giving Mifepristone was 124.6 ± 51.85 . It reduced to 34.72 ± 17.87 and the difference was found to be highly significant (Table 2). The Mean Uterine volume was $331.69 \pm 216.05 \text{ cm}^3$ and $239.68 \pm 157.23 \text{ cm}^3$ before and after giving Mifepristone respectively. The difference was found to be highly significant (Table 3). The Mean Volume of Leiomyoma was $68.62 \pm 38.94 \text{ cm}^3$ at the time study and after Mifepristone treatment, it was $46.71 \pm 27.96 \text{ cm}^3$. The difference was found to be highly significant (Table 4).

Table 1: Comparison of study population based on Dysmenorrhoea before and after giving Mifepristone

Dysmenorrhoea	Pre test (N)	Post test (N)	McNemar test	p-Value
Present	41	4	28.800	<0.0001
Absent	19	56		
Total	60	60		

Table 2: Comparison of the study population based on PBAC before and after giving Mifepristone

PBAC	Mean	Standard Deviation	Wilcoxon Test	p-Value
Pre-Test	124.6	51.85		<0.0001
Post-Test	17.87	34.72	-6.737	

Table 3: Comparison of the study population based on Uterine volume before and after Mifepristone treatment

Uterine Volume	Mean	Standard deviation	t-test	p-value
Pre-test	331.69	216.05		<0.0001
Post-test	239.68	157.23	11.215	

Table 4: Comparison of study population based on Leiomyoma volume before and after giving Mifepristone

Leiomyoma	Mean	Standard deviation	Wilcoxon test	p-value
Pre-test	68.62	38.94		<0.0001*
Post-test	46.71	27.96	-6.479	

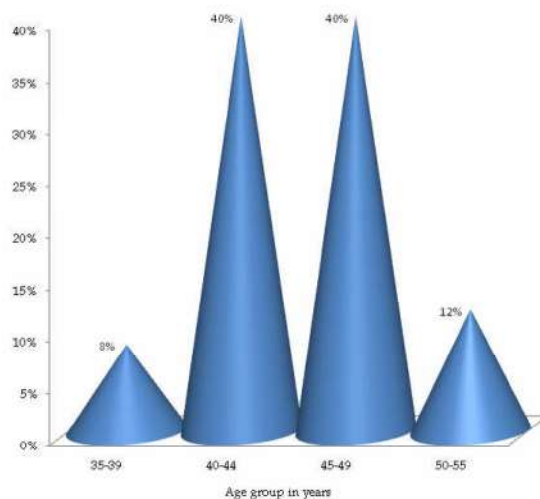


Fig. 1: Age-wise distribution of study population

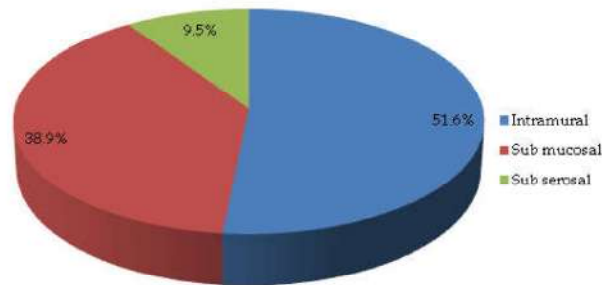


Fig. 2: Distribution of study population according to type of fibroid

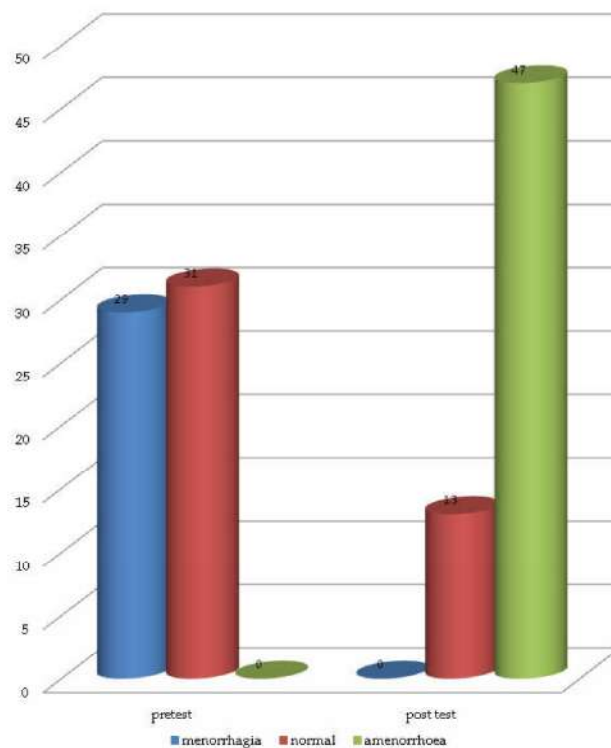


Fig. 3: Characteristic of Menstrual flow

In our study Menorrhagia was present among 29 study participants before starting the treatment. After 3 months of Mifepristone 10 mg/day, 47 study participants had Amenorrhoea and 13 had normal flow. There was significant association between Pre and Post test Menstrual flow (chi-square=12.85, $p < 0.0001$) (Fig. 3).

Discussion

In the present study, we have evaluated the effectiveness of Mifepristone in treating Uterine fibroids. Mifepristone is a progesterone receptor modulator which causes antiproliferative

endometrial effect, amenorrhoea and anovulation. Hence it has been used for the treatment of myoma, endometriosis and dysfunctional uterine bleeding.

We found that there was significant reduction in Dysmenorrhoea after taking Mifepristone for 3 months. This is similar to the findings in the study conducted by Hangarga US et al. conducted among 30 patients having uterine fibroid which showed vast improvement in Dysmenorrhoea after taking mifepristone [5].

In our study the mean value of PBAC was 124.6 which reduced to 17.87 after taking Mifepristone. The difference was highly significant. A study conducted by Murphy et al. showed similar result

where mean PBAC score reduced from 111.5 to 2.36 at the end of 3 months of therapy [6]. A similar study done by Kulshrestha V et al. showed that PBAC score reduced from 253 to 19.8 at the end of 3 months of therapy [7].

In this study the mean value of pre-test leiomyoma volume was 38.94 cm³ and post-test value was 27.96 cm³. The difference being highly significant, this was similar to the findings of a prospective interventional study done by Seema Saharan et al. that showed significant reduction in fibroid volume after 3 months treatment with Mifepristone [8]. The mean leiomyoma volume reduced by 35.7% in 3 months with 10 mg Mifepristone therapy in another study conducted by Kulshrestha V et al. [7] Another study conducted by Esteve JL et al. showed reduction in leiomyoma volume by 39.1% which was statistically significant [9].

The mean uterine volume in our study was reduced to 239.68 cm³ from 331.69 cm³ (28%). This difference was highly significant and similar to the study conducted by Fiscella et al. and Esteve JL et al. which showed significant reduction in Uterine volume after giving Mifipristone [10]. Another study conducted by Yang Y et al., using mifepristone 10 mg showed that mean uterine volume decreased by 41.4% after 3 months which was slightly higher reduction than that in our study [11].

In our study Amonorrhoea was experienced by 78% of the study participants after taking Mifepristone 10 mg for 3 months which was highly significant. A study by Fiscella et al. showed that 41% only experienced Amorrhoea which was lesser than that of our study [10] and another study done by Narvekar N et al., 100% of Amenorrhoea was achieved by the study participants after 3 months of treatment [12].

Conclusion

Our study shows that 10 mg of mifepristone is effective in reducing the size of Uterine leiomyoma which can help in accessibility during surgery and can reduce the chances of hysterectomy, thereby retaining fertility. It also showed decrease in the symptoms of Dysmenorrhoea and Menorrhagia whereby improving the general health status and quality of life of the study population.

Limitations

- This study includes only one group as control group could not be set up due to resource constraint.

- For generalization of results, a large population based study will be required.
- This study gives the result of 3 months follow up only. Longer duration follow up studies are required to see the long term effects of mifepristone.

Key Messages

Low dose of Mifepristone is effective in reducing the size of uterine leiomyoma

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Conflicting Interest (If present, give more details): Nil

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