

Effectiveness of Mifepristone in the Treatment of Uterine Leiomyomata

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Aims: The goal of this study was to determine the effects of mifepristone in perimenopausal women with leiomyomas, thereby to see a decrease in severity of symptoms and a decrease in size of the leiomyomas.

Methods: This was a prospective study conducted at Eden Hospital Medical College and Hospital, Kolkata from July 2010 to June 2011. Fifty patients received 20-25mg mifepristone daily and comparison was made between pre and post treatment symptoms and leiomyoma volume.

Results: All patients became amenorrhoeic after treatment, relieving heavy menstrual flow most complained of. Lower abdominal pain improved by > 80% in most patients and volume of leiomyoma decreased appreciably. The drug did not have any major side effects. Endometrial hyperplasia detected by ultrasound in 42% patients was only of simple type on biopsy.

Conclusions: Mifepristone can be useful in treating symptomatic women with uterine leiomyoma in perimenopausal age group, in those awaiting surgery to stop bleeding and improve anaemia and to reduce size of tumor to make surgery technically easier, making it a cheaper alternative to GnRH agonists and without any major side effects.

Keywords: fibroid, mifepristone, volume of fibroid, leiomyoma.

INTRODUCTION

Uterine leiomyomata or fibroids are common benign pelvic tumours and account for up to 40% of all hysterectomies.¹ Recent studies have shown the effectiveness of various modes of medical management for the treatment of uterine leiomyomas. The most widely used medical therapy is GnRH agonists, which have anti-estrogenic side effects and so cannot be used on a long term basis. Amongst the other drugs studied, anti-progesterone mifepristone is the most promising. Surgery and treatment with GnRH agonists have their own complications and are not always feasible.^{2,3}

Studies have suggested that leiomyomas growth is steroid-dependent and that mitotic activity in leiomyomas is greatest in the luteal phase.⁴ Recent studies have provided further biochemical, histological and clinical evidence that progesterone has a critical role in leiomyoma growth. Recently mifepristone, a progesterone receptor modulator with primarily antagonistic properties has been shown to decrease leiomyoma size.⁵⁻⁷

We studied the effects of mifepristone treatment on leiomyomas, specifically on the size of the leiomyoma and decrease in associated symptoms like pain and menorrhagia.

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METHODS

The study was conducted at Eden Hospital, Medical College and Hospital, Kolkata for a period of one year, commencing from July 2010 to June 2011. This study compared pre and post treatment leiomyoma volume and symptoms.

First ultrasound at the initiation of treatment noting the size and volume of fibroid and the endometrial thickness was done in all patients. Second ultrasound was done after three months of treatment with mifepristone recording the amount of decrease in fibroid volume and increase in endometrial thickness.

Patients with symptomatic uterine leiomyomas in premenopausal age without endometrial hyperplasia were included in the study. Women with systemic health problems like severe anemia and acute symptoms and those who used hormonal medication within three months of treatment initiation were excluded from the study.

In this study 50 patients with symptomatic leiomyomas were treated with 20-25 mg mifepristone daily for three months to note clinical improvement in symptoms and radiological decrease in fibroid volume. After this time period improvement in menorrhagia and pain lower abdomen were noted. Also recorded were the initial ultrasound volume of the fibroid and reduction in volume after three months of treatment. Development of untoward effects of mifepristone was also noted, namely endometrial hyperplasia. The information accumulated by treating 50 patients with mifepristone was then plotted in tables and charts for the ease of statistical analysis. Finally all the data was analysed to determine whether mifepristone caused any significant improvement in symptoms of patients or significant reduction in the volume of leiomyoma radiologically. McNemar Chi Square Test and Wilcoxon Signed Rank Analysis to determine the significance level of the study was done.

RESULTS

The commonest presenting symptoms of the patients were menorrhagia and pain lower abdomen. Though more than half of the patients had small fibroids with volumes < 100 cm³, 22% had quite large ones some even measuring > 500 cm³.

The study showed 100% improvement of menorrhagia as all the 34 patients with heavy bleeding were rendered amenorrhoeic during three months of treatment with mifepristone.

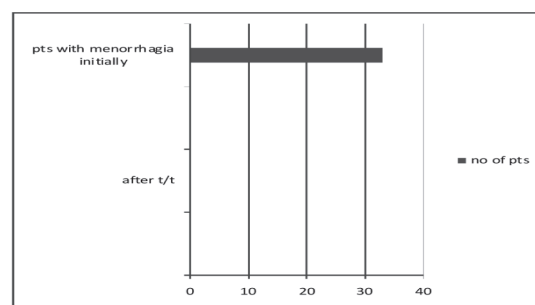


Figure 1. Bar diagram showing 100% improvement in menorrhagia in 34 patients presenting with excessive bleeding after 3 months of treatment with mifepristone.

Table 1 shows percentage of pain relief amongst the patients as determined by the pain analog score after three months of mifepristone use. Ninety percent of the patients reported reduction in pain of more than 40% and 67.9% had more than 80% decrease in pain.

Table 1. Improvement in pain lower abdomen or dysmenorrhoea (n=27).

Amount of pain reduction after mifepristone	Number of patients	Percent
0-20%	0	0%
21-40%	3	10.7%
41-60%	4	14.3%
61-80%	2	7.1%
81-100%	18	67.9%

Table 2 shows the percentage of reduction in leiomyoma volume after treatment as compared to the original volume. Almost 66% patients showed more than 80% reduction in fibroid volume as per ultrasound images.

Table 2. Reduction in the volume of leiomyoma (n=47).

Reduction in volume after mifepristone	Patients	Percent
0-20%	3	6.4%
21-40%	3	6.4%
41-60%	5	10.6%
61-80%	5	10.6%
81-100%	31	65.9%

Table 3 deals with the side effects of mifepristone, 42% of the patients showed endometrial hyperplasia (> 8 mm endometrial thickness). All patients of hyperplasia underwent biopsy and the histopathology showed simple hyperplasia.

Table 3. Patients with endometrial hyperplasia after 3 months of mifepristone (n=50).

Endometrial thickness	No of patients	% of patients
< or= 8 mm	29	58%
> 8 mm	21	42%

DISCUSSION

Mifepristone is effective in decreasing the severity of symptoms of leiomyoma and decreasing the volume of tumor. The present study also determined the effectiveness of this drug in treating uterine leiomyoma and compares the result to those obtained previously. The presenting symptoms of our patients were variable with 40% presented with only menorrhagia, 26% with lower abdominal pain and 28% complained of both heavy bleeding and pain. Overall 68% presented with increased bleeding per vagina, corroborating the fact that abnormal bleeding is the commonest symptom of leiomyomas.

There was a huge improvement in this symptom as all 34 patients with menorrhagia became amenorrhoeic after 3 months of treatment with mifepristone. Pallor improved and the patients felt a sense of well-being. They were counselled about this effect of mifepristone and were assured that their menstrual function would resume after stoppage of treatment. The finding of 100% amenorrhea in this study corroborates with all previous studies^{8,9} using mifepristone > or = 20 mg daily.

The patients were initially asked to rate the amount of pain they felt on a scale of 1 to 10 (pain analog score) and the procedure was repeated after three months of treatment and 68% of the patients reported a subjective improvement of 81-100% by this scoring system and 94% recorded some amount of improvement.

Table 4. Comparison with various other studies.

First Author	Mifepristone Dose (mg)	% of reduction in volume of fibroid
Murphy ¹⁰	50	49 +/- 9
Murphy ¹¹	25	56 +/- 5
Reinsch ¹²	25	32
Yang ⁸	20	33
Zeng ⁹	12.5	74
Engman ¹³	25	28
Present Study	25	80

The most important objective criteria to prove the efficacy of this drug was ultrasonographic reduction in tumour volume. Initially the volume was calculated using the formula $4/3\pi abc$, where a, b and c are the diameters of the fibroid in three dimensions. After three months of treatment volume was recalculated and reduction in volume was noted. Ninety-four percent of patients showed some reduction in the volume of leiomyoma with 66% patients showing a reduction of 81-100%. Other studies¹⁰⁻¹² have also shown reduction in fibroid volume by up to 87%. A statistical analysis of this data by Wilcoxon Signed rank Test showed a p value of <0.001. Only 3 of the 50 patients showed radiological increase in the volume of leiomyoma. Of them two underwent hysterectomy later in which the gross specimen did not show any evidence of the presence of leiomyoma, but both had large adenomyotic uteri. The mean % of reduction in volume was 80% (Table 4), which is much higher than previous ones, but almost corresponds to the study by Zeng.⁸

Total 42% of the patients (Table 3) developed endometrial hyperplasia according to the ultrasound report, with endometrial thickness >8mm. Previous studies^{12,13} have also showed this effect, with the number of patients developing endometrial hyperplasia increasing as the dose of mifepristone was increased from 5 to 25mg daily. All the patients were biopsied and the histopathology report showed simple hyperplasia only.

Though this study had some methodological disadvantages, i.e., small sample size, non-randomized and without any control arm like treatment with GnRH agonist, but it definitely showed that mifepristone causes both clinical and radiological improvement for uterine leiomyomas.

CONCLUSIONS

Mifepristone can be useful in treating symptomatic women with uterine leiomyoma in the perimenopausal age group, in patients with menorrhagia awaiting surgery to improve anemia, and to reduce the size of tumors to make the surgery technically easier.

Additionally this drug is cheaper than GnRH agonists. So it definitely shows promise of emerging as an alternative medical therapy for perimenopausal women and women with menorrhagia and pallor waiting for surgical intervention. Whether it can be used for all patients on a long term basis and the probability of recurrence of fibroids after stopping the drug needs to be evaluated further with larger randomized controlled trials.

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