



STUDY TO EVALUATE EFFECTS OF MIFEPRISTONE 25mg IN MANAGEMENT OF UTERINE FIBROIDS

Obstetrics And Gynaecology

Dr Nidhi Johri Assistant Professor, Department of Obstetrics and Gynaecology Saraswati Medical College.

Dr Priti Kumar* M.B.B.S., M.S. (Obs & Gyne). Professor, Department of Obstetrics and Gynaecology Naraina Medical College and Research Centre, Kanpur. *Corresponding Author

ABSTRACT

Background: In India, the uterine fibroid is a common indication of hysterectomy. An effective option for medical treatment may decrease the morbidity associated with hysterectomy.

Objectives: We aimed to evaluate the effect of mifepristone (25 mg), progesterone antagonist, on uterine fibroids in perimenopausal women. **Material And Methods:** Fifty perimenopausal women having symptomatic uterine fibroids were selected from Gynaecology OPD and given 25 mg mifepristone once daily continuously for 2–4 cycles of 3 months each. Variables such as baseline fibroid size, position, and haemoglobin were measured and followed at 3, 6, 9, and 12 months. The data were entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0. A P value of <0.05 was considered as statistically significant.

Results: Majority were intramural fibroids (70%) followed by submucosal in 18%. Size of fibroids ranged from 7 cm; the majority of fibroids were in 5–7 cm size. No significant association of location with the size of fibroid was found. Out of 50 cases included in the study, change in size in uterine fibroids was observed in 95.14% cases. There was an increase in haemoglobin, from 8.6 g% at baseline to 9.5 g% at 12 months.

Conclusion: Mifepristone resulted in a reduction in uterine fibroids size and an increase in haemoglobin at the end of 12 months. It may be an option for uterine leiomyoma treatment, as it is given orally, cost-effective and has minimal side effects.

KEYWORDS

Fibroid, Medical Management, Mifepristone

BACKGROUND:

Uterine fibroids (UFs), known as uterine leiomyomas, are benign smooth muscle neoplasms of the uterus affecting women of reproductive age.[1] UF occur in 70% of women by the onset of menopause.[2] They are estimated to be clinically apparent in 25% of women of reproductive age.[3] Although they are often asymptomatic, UF can cause symptoms such as menorrhagia, abnormal uterine bleeding, pelvic pain or pressure, infertility, and recurrent pregnancy loss.[4]

Larger fibroids sometimes push the bladder or bowel and cause an increased urge to urinate or digestion problems (constipation, pain), and cause obstruction of the ureters impeding to the immediate treatment.[5] In clinical practice, for the treatment of fibroids, surgical treatments are used effectively. Surgical treatments are preferred as the last resort by the patients because none of the surgical treatments, other than hysterectomy, offer a recurrence-free survival.[5] However, during the current practice, the authors themselves have been consulted by many patients who are afraid of surgery and want a medical treatment for the fibroids. Medical treatment seems easier to be adopted, inculcates less fear, and is on a cheaper side. This has led to the practicing physicians to prescribe certain drugs for selective treatment of fibroids.

Aim And Objectives:

Current study was done to evaluate the effects of medical therapy (mifepristone 25 mg) on the management of uterine fibroids among perimenopausal women.

MATERIAL AND METHODS:

It was a prospective interventional study which was conducted in the department of Obstetrics and Gynaecology over a period of 1 year (31st January 2019 to 30th January 2020) where women with uterine fibroids were enrolled for medical management after informed medical consent. The study was approved from the institutional ethical committee of the hospital. A written informed consent was taken from all the patients enrolled in the study as per the inclusion and exclusion criteria.

Inclusion Criteria:

- 1) Patients in peri menopausal age group.
- 2) Diagnosed fibroid cases
- 3) Fibroid size ≥ 2.5 cm
- 4) Patients who were on contraceptives must have accepted the use of nonhormonal contraceptives.
- 5) Patients who agreed to have an ultrasound examination in every follow-up or evaluation visit.

Exclusion Criteria:

- 1) Pregnancy
- 2) Undiagnosed cause of irregular bleeding PV
- 3) Underlying any other metabolic, hepatic, or renal complication All included participants underwent Pap smear (excluding unmarried women), endometrial evaluation by pipelle or aspiration in all married women >35 years, Hb levels, CBC, S. ferritin levels, TSH, serum prolactin levels, and TVS/USG for fibroid size and location and the endometrial thickness.

RESULTS:

Mean age of the patients in the study was 47.56 years. Most of the patients (36%) were of >51 years age, followed by 30% patients in 48–51 years age group. Total 90% of patients were married [Table 1].

Chief complaints of the study subjects were menorrhagia in 79% and heaviness in lower abdomen in 6% of patients. Total 15% of patients were asymptomatic.

The intramural fibroid was the most common (70%) followed by submucosal (18%) and subserosal (12%) fibroids. Size of most of the fibroids (34%) was 5–7 cm, followed by 30% having tumor size 3–5 cm and 20% having size <3 cm [Table 2].

Table 1: Demographic Characteristics Of Study Population

Characteristics	No.	Percentage %
Age in years		
40-43	07	14%
44-47	10	20%
48-51	15	30%
>51	18	36%
Mean $\pm$ SD		
Marital status		
Married	45	90%
Unmarried	05	10%

Table 2: Distribution And Size Of Fibroid

Location	No.	Percentage %
Subserosal	06	12%
Intramural	35	70%
Submucosal	09	18%
Size in cm		
<3	10	20%
3-5	15	30%
5-7	17	34%
>7	08	16%

Table 3: Change In Size Of Fibroid At Different Time Intervals.

Change in size	3 months	6 months	9 months	12 months
No change	05 (10%)	03 (6%)	02 (4%)	01(2%)
0.5-0.9cm	15 (30%)	12 (24%)	12 (24%)	14 (28%)
1-1.4cm	20 (40%)	25 (50%)	25 (50%)	23 (46%)
1.5-1.9cm	07 (14%)	05 (10%)	06 (12%)	07 (14%)
>2cm	03 (6%)	05 (10%)	05 (10%)	05 (10%)

At 3 months, there was no change in size in 10% patients. At 12 months, one patient (2%) had no change in tumour size. At 3 months, 0.5–0.9 cm change was noted in 30% patients; total 28% patients had 0.5–0.9 cm change at 12 months. A change of 1–1.4 cm in size was noted in 40% patients at 3 months, which increased to 46% patients at 12 months. Change in size of 1.5–1.9 cm was in 14% patients at 3 months and was similar 14% patients at 12 months. More than 2 cm change was present in 6% patients at 3 months and 10% patients at 12 months [Table 3]. At presentation, mean haemoglobin was 8.6 (g%) that increased to 9.7 (g%) at 12 months after the medical treatment.

DISCUSSION:

Although curative treatment for UF relies on surgical therapies, medical treatments are considered as the first-line treatment to preserve fertility and avoid or delay surgery.[8,9] In the index study, we found that medical management (mifepristone 25 mg) was effective in reducing the size of the small to medium fibroids. Our findings are supported by a recent analysis in the treatment of UF over a period of 2004–2018 by data mining technology and the medication rule which showed that among the common clinical drugs including leuporelin (GnRH-a), danazol (androgen), gestrinone (progestin), mifepristone (progesterone receptor antagonist), and some cases of combination therapy, the clinical use of mifepristone was the commonest with mild drug reactions and thus was worthy of clinical use and application.[7] The substantial effects of mifepristone are based on the combination effects on the estrogen, progesterone, and androgen regulators.

The reduction in size of fibroids with mifepristone can be attributed to the direct effect in decreasing the number of progesterone receptors, and creating an early pressure symptoms.[8] Mean age was 38.47 years in the study by Seth et al.; abnormal and excessive uterine bleeding (AUB) was the commonest problem reported, followed by heaviness in lower abdomen and pain for which they came to the hospital.[10] Raghav et al. reported that the mean age of the patients was 39.40 years with main symptoms being menorrhagia followed by those having polymenorrhea, intermenstrual bleeding, polymenorrhagia, abdominal pain, and dysmenorrhea.[6]

On advocating treatment with mifepristone 25 mg, no reduction in size was seen in one of the fibroids in the duration of 12 months. The increased duration of the medical treatment led to an increased reduction in the size of the fibroid. At 12 months after treatment, >2 cm reduction in size was found to be increased as compared to 3-month, 6-month, and 9-month duration. As compared in Saxena et al. (2019), there was 85.08% reduction in multiple myomas and 79.11% reduction in single myomas.[12] An increase in hemoglobin was found after 12 months of treatment as compared to baseline.

Our results are comparable to that of previous studies. Kulshrestha et al. and Jain reported that there was a significant rise in hemoglobin levels with a dose of 25 mg ($P < 0.05$).[11] The duration of treatment with mifepristone has been a variable factor depending upon the dose of mifepristone.

Two doses have been tried 10 mg and 25 mg. The previous studies with mifepristone reported lesser efficacy with doses of 10 mg. It was concluded that for causing a clinically significant (50%) reduction in leiomyoma volume, an effective dose was 25 mg daily.[13] Saxena et al.(2019) found both doses to be effective in the reduction of myoma size, with 25 mg showing better pain reduction and overall symptoms improvement in case of failure in response with 10 mg.[12]

CONCLUSION:

Mifepristone caused a reduction in the size of uterine fibroids in 95.14% cases and a simultaneous increase in haemoglobin levels till the end of 12 months. Thus, mifepristone 25 mg is effective in reducing the size or complete curing of the fibroids and can be used as a surgical substitute in patients who have fibroid associated anaemia, small to medium fibroids, women who want to preserve uterus and in cases

where leiomyoma are unresectable, or surgery is difficult. It may be an option for uterine leiomyoma treatment in perimenopausal age group, as it is given orally, cost-effective and has minimal side effects.

Acknowledgement:

We extend our sincere thanks to Dr. Abhishek Arun (MD) for his assistance in medical writing. We are also thankful to junior doctors and staff of Obs and Gynae department Saraswati Medical College and Naraina Medical College. Special thanks to everyone who participated in the study.

Limitations:

As it is a single centre study with a relatively small study population, results cannot be generalized to the entire population. The outcomes of the medical management were not compared with the surgery outcomes. Even variable doses of mifepristone were not compared during the study.

REFERENCES:

- Boosz AS, Reimer P, Matzko M, Romer T, Muller A. The conservative and interventional treatment of fibroids. *Dtsch Arztebl Int* 2014;111:877-83.
- Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. *Int J Gynaecol Obstet* 2020;149:3-9.
- Taylor DK, Holthouser K, Segars JH, Leppert PC. Recent scientific advances in leiomyoma (uterine fibroids) research facilitates better understanding and management. *F1000Res* 2015;4(F1000 Faculty Rev):183.
- Shen Q, Hua Y, Jiang W, Zhang W, Chen M, Zhu X. Effects of mifepristone on uterine leiomyoma in premenopausal women: A meta-analysis. *Fertil Steril* 2013;100:1722-6.
- Khan AT, Shehmar M, Gupta JK. Uterine fibroids: Current perspectives. *Int J Womens Health* 2014;6:95-114.
- Raghav V, Singh Y, Shankar P, Dixit RK. Role of mifepristone in conservative management of fibroid uterus. *World J Pharm Sci* 2016;4:118-24.
- Xuan J, Deng G, Liu R, Chen X, Zheng Y. Analysis of medication data of women with uterine fibroids based on data mining technology. *J Inf Pub Health* 2019. doi: 10.1016/j.jiph.2019.07.017.
- Jain D. Mifepristone therapy in symptomatic leiomyomata using a variable dose pattern with a favourable outcome. *J Mid-life Health* 2018;9:65-71.
- Sohn GS, Cho S, Kim YM, Cho CH, Kim MR, Lee SR; Working Group of Society of Uterine Leiomyoma. Current medical treatment of uterine fibroids. *Obstet Gynecol Sci* 2018;61:192-201.
- Seth S, Goel N, Singh E, Mathur AS, Gupta G. Effect of mifepristone (25 mg) in treatment of uterine myoma in perimenopausal woman. *J Midlife Health* 2013;4:22-6.
- Kulshrestha V, Kriplani A, Agarwal N, Sareen N, Garg P, Hari S, et al. Low dose mifepristone in medical management of uterine leiomyoma-an experience from a tertiary care hospital from north India. *Indian J Med Res* 2013;137:1154-62.
- Saxena R, Goyal R, Jain R. Effects of low dose oral mifepristone on uterine fibroids. *Indian Obs Gyn* 2019;9:38-42.
- Murphy AA, Morales AJ, Kettel LM, Yen SSC. Regression of uterine leiomyomata to the antiprogesterone RU 486 dose response effect. *Fertil Steril* 1995;64:187-90.