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Original Article

A randomized control trial to assess efficacy of Mifepristone in medical management of uterine fibroid

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ABSTRACT

Background: Fibroids are the most common benign tumours of uterus. Heavy menstrual bleeding is the commonest concern for which medical attention is sought. Hysterectomies for leiomyoma constitute a third of all hysterectomies. Thus, healthcare cost to society due to uterine leiomyomas is of considerable importance.

Methods: A prospective study was conducted at tertiary care hospital of armed forces. 120 women in pre-menopausal age group with complaints of menorrhagia, Pictorial Bleeding Assessment Chart (PBAC) scoring ≥ 100 and at least one fibroid ≥ 2.5 cm in size were recruited in the study. Patients in Group 1 were given Tab Tranexemic acid (500 mg) and Tab Mefenemic acid (500 mg) three times a day during menstrual bleeding for a period of 6 months. Patients in Group 2 were given Tab Mifepristone 50 mg twice a week. They were followed up at 1, 3 and 6 months of starting the medicine. Results were statistically analysed using Microsoft Excel sheet and paired t-test.

Results: The average age was 40 years in the Group 2 and 45 years in Group 1. A size reduction of 36.99% in intramural and 39.39% in submucosal fibroids after six months of treatment with Mifepristone resulted in marked clinical improvement. 10% patients had side effects. In 30% of patients symptoms reappeared during the follow up period.

Conclusion: Mifepristone when given in bi-weekly doses was found to be safe, efficacious, and cost effective as compared to treatment with tranexemic acid and mefenemic acid for management of fibroid uterus.

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Introduction

Uterine myomas (fibroids) are the most common benign tumours found in up to 70% women during their reproductive years.¹ Although many women with fibroids are asymptomatic, others find they cause a major disruption to daily life. Malignant transformation in uterine fibroids is seen in only less than 0.1% of cases. The main associated symptoms are often problematic like heavy menstrual bleeding (HMB)^{2,3} that may result in severe anaemia and social embarrassment and the presence of a pelvic mass may lead to marked discomfort, abdominal distension, and pressure-related bladder symptoms. Additionally, distortion of the uterine cavity may result in sub-fertility.⁴ Approximately 20–40% of these uterine tumours are symptomatic in premenopausal women accounting for 20–80% of hysterectomies in these women.^{5–7}

Treatment modalities for fibroids comprise of medical and surgical methods. Though medical methods are easier, availability and cost are the limiting factors. Surgery has always been considered as the final treatment. Various minimally invasive techniques such as catheter guided embolization of myoma feeding vessel or laparoscopy performed to conserve uterus are still beyond reach for most patients. Thus the individual discomfort and the healthcare cost for society due to uterine leiomyoma is of significant importance.

There is biochemical, clinical, and pharmacological evidence to support a role for progesterone in the pathogenesis of fibroids. Hence, the use of antiprogestins like Mifepristone for medical treatment of myomas was an obvious development. Seth et al. found 25 mg Mifepristone administered daily for 3 months resulted in substantial improvements in leiomyoma specific quality of life, bleeding, and leiomyoma size.⁸ The concerning side effects are reversible like endometrial hyperplasia,⁹ elevated liver functions and others such as abdominal pain, nausea, vomiting, diarrhoea, headache, hot flushes, occasional body-aches. Data suggest that many invasive procedures could be avoided with the routine use of Mifepristone for fibroid tumours care.

With promising results seen with this drug, experiments started with higher doses of Mifepristone. Various studies support the use of Mifepristone (50 mg administered every other day) has effectively resulted in a significant reduction in leiomyoma size, reduced uterovaginal bleeding and increased blood haemoglobin. A potential disadvantage with higher doses of Mifepristone is its antiglucocorticoid effect. Earlier studies have also reported that the changes seen in the endometrium are reversible on discontinuation of treatment.

This study was done to assess the efficacy of Mifepristone in a twice weekly dose of 50 mg for six months. The study also evaluated reversibility of endometrial hyperplasia at six months after cessation of therapy, change in the haemoglobin and the side effects of the drug.

Material and methods

Study population

Patients visiting the outpatient department (OPD) of Department of Obstetrics and Gynaecology of our hospital with complaints of HMB were initially enrolled.

Patients with the following criteria were then, excluded from study:

Current planned pregnancy during study period

Menopausal

Currently breastfeeding

Untreated abnormal pap smear

Presence of conditions other than fibroids contributing to pain and/or bleeding

Hb < 6.0 g/dl

Presence of adnexal mass or tenderness indicating further evaluation of surgery

Grade III/IV hydronephrosis

Endometrial hyperplasia

Presence of any contraindications to Mifepristone including:

- adrenal insufficiency in history
- sickle cell anaemia
- active liver disease (Liver Function Test (LFT) > 1.5 times upper range of normal)
- Severe respiratory disease (SpO₂ < 90%)
- Renal disease (S.creatinine > 1.5 mg/dl)
- Blood clotting defect (abnormal Prothrombin Time/Partial Thromboplastin Time in Kaolin/International Normalisation ratio (PT/PTTK/INR))
- Thromboembolic disease (History of (H/O) Deep Vein Thrombosis (DVT)/pulmonary embolism)
- H/O allergic reaction to Mifepristone
- Inherited porphyrias
- Presence of any valvular heart disease

Current or recent (within 3 months) use of the following:

- Oral/systemic corticosteroids
- Hormones (E/P/Oral Contraceptive Pills (OCPs))
- Danazol
- Anticoagulant

Use within past 6 months of GnRH analogues

Current/planned use during the study of medications:

- Ketoconazole
- Itraconazole
- Erythromycin
- Phenytoin
- Phenobarbital
- Carbamazepine
- Rifampicin

Total of 120 women in pre-menopausal age group with complaints of menorrhagia, Pictorial Bleeding Assessment

Chart (PBAC) scoring ≥ 100 and with at least one fibroid ≥ 2.5 cm in size were recruited in the study. An informed consent was taken, after explaining the treatment protocol to selected patients.

Sample size calculation

Since this was a pilot randomized control trial comparing two modalities of treatment, sample size calculation is not indicated.

Study design

The study protocol was approved by the institutional ethics and health research committee as a prospective, parallel,

randomized, controlled, interventional clinical trial. All eligible patients prior to recruitment were explained about the study in detail. Written informed consent for participation in the study was obtained. The numbers on the envelopes of medicines were assigned in the pharmacology laboratory by the lab staff while packing the medicines. The packaging also contained instructions on how to take the medication. After confirming eligibility the patients were referred to an intern who gave away the medicines packed identically and in numbered envelopes, after noting the number of the pack against the name of the patient. Patients were randomized into two groups, Group1 and Group 2, as per a computer generated sequence that was placed in sequentially numbered, opaque, sealed envelopes. This ensured allocation concealment. The doctors subsequently following up these

patients were, thus, blinded to their allocation to Group 1 or Group 2.

The patients in Group 1 were given Tablet Tranexemic acid (500 mg) and Tablet Mefenemic acid (500 mg) three times a day during menstrual bleeding for a period of 6 months. They were asked to make a note of any side effects. The patients were followed up at 3 month and 6 months period. The patients in Group 2 were given Tab Mifepristone 50 mg twice a week. The drug, a 200 mg tablet was dispensed after being changed into powdered form (using mortar and pestle) and then divided into 4 equal parts and dispensed in pouches each containing 50 mg of the drug (using the weighing scale in pharmacology laboratory). The patients were asked to take this pouch twice a week for 6 month and were called for review in the OPD of hospital at 3 and 6 months of starting the medicine.

To ensure uniformity all patients were asked to start medication from the first day of the menstrual cycle.

Pre and post-randomization care of patients

All patients prior to randomization were subjected to detailed history, clinical examination and investigations such as hematocrit evaluation, peripheral blood smear for typing of anaemia, coagulation profile, liver and renal function tests, thyroid profile, Pap smear, pelvic and renal ultrasonography and endometrial biopsy.

After randomization to Group 1 and Group 2, the follow up visits were scheduled at 3 and 6 months. Patients were asked to report earlier in case of any shortness of breath/rash/swelling of lips/choking sensation/hives or itching and stop the drug immediately. The patients were counselled about the possible side effects like uterine cramping, abdominal pain, nausea, vomiting, diarrhoea, headache, hot flushes, occasional bodyache and any other complaints.

All patients were subjected to transvaginal ultrasonography and re-evaluated at three months and six months interval to assess changes in size and appearance of fibroids, changes in menstrual pattern, endometrial thickness, haemoglobin levels and blood loss assessment by pictorial blood loss assessment chart. The largest dimensions of the fibroid in two planes were measured. These two dimensions were multiplied with each other to calculate the area of the fibroid: (Area of fibroid = dimension 1 × dimension 2).

Efficacy

The primary variable considered for efficacy was menstrual bleeding which was assessed by means of a PBAC score. The patients on review visit at six months were asked to fill a feedback form in which they reported number of days of menstrual bleed, number of tampons used after beginning of treatment, whether bleeding had increased or decreased post treatment, and by how much. The individual PBAC score was calculated based on this feedback.

Secondary variable for efficacy was reduction in area of fibroid, determined as a product of length and breadth of the myoma, measured on ultrasound.

Statistical analysis

The results were statistically analysed using Microsoft Excel sheet and independent 't' test.

Data for all quantitative variables are presented as mean ± standard deviation. Parameters for safety or complications were analysed on the basis of actual treatment received.

Results

The age group involved in the study was from 18 years till premenopausal. Table 1 reflects the average age was around 44 years in the Group 2 while it was around 45 years in Group 1. Approximately 63% were having intramural fibroids, 33% submucosal fibroids and 3% subserosal fibroids. In study group, majority of the patients had the fibroid size between 4 cm × 4 cm and 6 cm × 6 cm whereas, in the control group patients with fibroid size less than 4 cm × 4 cm were more in number. All of our patients had HMB as the primary symptom, the severity of which was scored as per the PBAC scoring system. It was observed that with Mifepristone all patients without exception had amenorrhoea bringing this score to 'zero'. The average reduction of symptoms in Group 1 (subjective as per patient) was approximately 50%.

On transvaginal ultrasonography it was found that in the Group 2, the mean fibroid area at the beginning of the study was 8.95 cm². After 6 months of taking Tablet Mifepristone, significant reduction in all dimensions of fibroid leading to an overall reduction in area was observed ($p = 0.001$). The mean area after 6 months treatment was found to be 5.65 cm² (Table 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 Group 1 (Tables 2 and 3).

In Group 2, immediate reduction in vaginal bleeding was observed and all patients attained amenorrhoea within few days of starting the treatment (after 2nd/3rd dose) with sudden improvement in the general health. As per the analysis done as well the change in haemoglobin observed over the treatment course was significant statistically (Table 2).

It was observed that after 06 months of treatment with Tab Mifepristone the average endometrial thickness was 7.34 mm. 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. In the sub-groups of intramural and sub-mucosal fibroids the endometrial thickness was found to be 7.36 mm and 7.44 mm respectively. This difference was significant.

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 (Table 4).

It was noted that in the study population, 02 patients had to discontinue with the treatment due to deranged liver function test. Apart from that 06 patients had minimal side-effects like hair fall, headache and puffiness of body. It was concluded that 13.3% patients in the Mifepristone group, had side-effects. But

Table 1 – Baseline characteristics of the study population.

Criteria	Group 1 (Mean)	±SD ^a	Group 2 (Mean)	±SD ^a	p value
Age (in years)	45.1667	5.5837	44.0333	8.4669	0.513
Area of fibroid (in cm ²)	8.2967	3.0598	8.9567	3.4793	0.438
PBAC ^b score	141.333	42.5671	154.5000	50.5206	0.276
Hb ^c (in g/dl)	10.1667	0.6910	9.6633	1.6504	0.432

^a SD: standard deviation.
^b PBAC: pictorial bleeding assessment chart.
^c Hb: haemoglobin.

Table 2 – Group 1: comparison between initial and final parameters.

Paired samples statistics					
		Mean	N	S	Std. error mean
Pair 1	INITIAL HB	10.07	60	.686	.089
	HB 6 MTH	10.13	60	.724	.093
Pair 2	FIBROID area (CM)	20.45 ^a	60	16.015	2.068
	AREA @ 6m	20.45 ^a	60	16.015	2.068

Table 3 – Group 2: comparison between initial and final parameters.

Paired samples statistics					
		Mean	N	SD	Std. error mean
Pair 1	FIBROID area (CM)	22.18	60	17.093	2.207
	AREA @ 6m	10.57	60	9.893	1.277
Pair 2	INITIAL HB	9.69	58	1.698	.223
	HB 6 MTH	10.52	58	1.513	.199

Table 4 – Changes in the study population at three and six months.

Criteria	Initial		3 months		6 months	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Area (in cm ²)	8.2967	8.9567	8.2967	7.1333	8.2967	5.6533
Hb (in g/dl)	10.1667	9.6633	10.1767	10.0900	10.1600	10.1600
ET (in cm)	6.18	6.36	6.15	7.20	6.16	7.34
PBAC score	141.333	154.500	140.987	124.746	140.860	112.030

these side-effects were not of that severity that it affected the quality of life of the patients.

After the full course of treatment, the symptoms reappeared in 18 patients (30% patients) to an extent that they had to resort to alternative modes of treatment as 02 patients had levonorgestral intrauterine system insertion and 16 patients underwent hysterectomy.

Discussion

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 years which is similar to other studies in literature thereby suggesting that a large number of pre menopausal women are in need for treatment of symptomatic leiomyomas.

In the study conducted by Carbonell Esteve et al.¹⁰ 90% women had achieved amenorrhoea. As per the study of Niger Med Journal with 25 mg Mifepristone daily for 6 months,

amenorrhoea was attained by 75% patients. Treatment with 5–10 mg Mifepristone for one year led to amenorrhoea in 40–70% patients while 100 mg daily dose of Mifepristone led to 100% amenorrhoea.¹¹ In our study the percentage reduction in pictorial blood assessment chart during six months treatment course was 100% because all women in the test group achieved amenorrhoea. Whereas, in the control group tranexemic acid and mefenemic acid led to approximately 50% reduction in the PBAC score. This reduction in the score was statistically significant (p -test = 0.001). Moreover, all our study subjects were satisfied with the relief of menstrual symptoms at 6 months and were even willing to continue the treatment. Primarily, this study was an attempt to measure the symptomatic relief provided by Mifepristone and not to measure its efficacy to reduce fibroid size.

The results of our present study show a statistically significant reduction in mean fibroid area (average reduction of all myomas was 37.07%; 36.99% in intramural and 39.39% in sub-mucosal group). Reports from Niger Med Journal 2011¹² suggested a decrease in fibroid size up to 47%. Similar findings were published in F1000Medical reports in 2009 by Kirsty et al.¹³ where with the dose of 5 mg or 10 mg Mifepristone for 6 months, size reduction of 50% was observed.

In our study, immediate reduction in menorrhagia was observed and improvement in overall health was evident, but the rise in haemoglobin after 6 months of treatment was slow and not significant. Bagaria et al.¹⁴ in 2009 had shown an increase in haemoglobin level which is comparable to our study outcome.

During the course of our study serial transvaginal sonography were done to measure endometrial thickness, since endometrial hyperplasia is a known entity with anti-progestones. It was observed that after six months of treatment with Mifepristone the average endometrial thickness was 7.34 mm. Among the side effects, elevated hepatic enzymes were found in 3.3% patients and minor ailments in 10% patients. In the study by Malartic et al.¹⁵ with 5 mg daily dose of Mifepristone, elevated hepatic enzymes were found in 4% patients, endometrial hyperplasia in 28% patients and hot flushes in 38%. Thus, the reduced frequency of the dose in our study might have contributed in minimizing the side effects.

During the follow up period, after full course of treatment the symptoms reappeared in 30% patients to such a severity that they had to resort to other modalities of treatment.

Conclusion

Various studies conducted worldwide have proven that Mifepristone is certainly a drug with promising results and has given unparalleled satisfaction to myoma patients. The only question that remains is the appropriate regimen (dose, frequency and duration) so as to achieve high patient compliance and satisfaction with minimal side effects. Our study has achieved 100% amenorrhoea in all patients during the course of treatment, which was statistically significant. There was marked clinical improvement in symptoms and sense of well being felt by the patients. Marked reduction in

fibroid size had reduced the PBAC score over six months of treatment. The high compliance rate in our study could be due to the drug being issued to the patients free of cost.

Mifepristone 50 mg biweekly was found to be safe, efficacious and feasible with good patient satisfaction rates. We recommend more multicentric randomized trials with long term follow up and larger study population to define the duration of therapy.

Conflicts of interest

The authors have none to declare.

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