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ROLE OF MIFEPRISTONE IN THE TREATMENT OF UTERINE FIBROID

Nidhi Patel, Wansalan Karu Shullai* and Garima

India.

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***Corresponding Author**
Wansalan Karu Shullai
India.

ABSTRACT

AIM: To assess safety and efficacy of Mifepristone (50 mg daily for 6 months) on fibroid size, endometrium and symtoms related to fibroid. **Material and method:** Study was carried out in Sir Sunderlal Hospital BHU. 55 patients were randomly assigned into two groups: group M(mifepristone group), group C (control group). Main outcome measure included efficacy aspects viz mean myoma volume reduction, mean hemoglobin rise, reduction in frequency and grading symtoms. All the parameters were recorded at baseline and every 2 months till the duration of study is completed. Post treatment measurements were carried out 6 months off the drug treatment. **Result:** ● Mifepristone causes 46.6% reduction in fibroid volume compared to baseline(p=0.007). ● Leads to significant rise in hemoglobin and marked improvement of symptoms related to fibroid. ● Endometrial thickening was significantly increased, but none reported atypia. ● Cases in M groups reported rise in myoma size, reaching the baseline values in 6 months follow up period. Conclusion: ● Drug results in reduction in size of fibroid, but the effect is not static. ● Administering 6 months treatment with mifepristone achieves symptomatic improvement lasting upto 6 months in high percentage of cases. ● More studies need to be carried out with both the drugs for longer period of time.

KEYWORDS: fibroid size, endometrium and symtoms.

INTRODUCTION

The prevalence of Uterine leiomyomas (fibroids or myomas) is as high as 25% in women of the reproductive age group. Despite the frequency of these tumors in women and the morbidity that they cause, leiomyomas remain a true frontier for gynaecologic investigation. Epidemiologic risk factors for leiomyomas, including black race and increasing age before menopause, have recently been described. The disciplines of epidemiology, genetics and biology have recently contributed greatly to our understanding of leiomyomas. The

pathogenetic mechanisms of leiomyoma initiation are still unknown. Important advances have been made in medical management but predominant treatment remains surgical.

MATERIAL AND METHOD

This study was a prospective clinical trial conducted after getting approval by the Ethical and Scientific committee IMS BHU. Subjects were recruited from gynaecological OPD of SIRSUNDERLAL HOSPITAL, BHU. Women in reproductive and perimenopausal age group were eligible for the study. Asymptomatic uterine fibroid >2.5 cm or Symptomatic uterine fibroid of any size were included in study. Patients with Pregnancy or desirous to become pregnant, Breastfeeding, Hemoglobin <8, Sign or symptoms of PID, Adnexal mass, unexplained vaginal bleeding, suspected or undiagnosed malignancy, Mental illness, Hepatic/renal disease/adrenal disease, Coagulopathy. Sickle cell anemia, Hormonal contraception or any hormonal therapy received in last three months and contraindications to antiprogesterones, were excluded from study.

Group M (mifepristone)- 50 mg/day taken orally over 6 months. Treatment begin chronologically as patients joined the study.

Group C (control)- patients didn't receive any drug.

Complete gynaecological examination and abdominal or vaginal ultrasound of the uterus was performed before the start of the study, again 3 and 6 months into treatment. Fibroid volume was calculated using the formula: 4Pabc/3 where a, b and c are the radii of the spheres in each of the three planes and are expressed in cubic centimeters. If the subject had more than one myoma, the measurement of the biggest was taken and its variations were used to evaluate efficacy. Ultrasonography was used to calculate endometrial thickness in mm. Blood samples were taken for hematological tests and hepatic tests every 2 months during treatment. subject presenting alterations in transaminases three times or more above their normal maximum limit, in line with FDA recommendations, would be dropped from the study. In Mifepristone group endometrial biopsy was performed before and after treatment in all subjects except those who had had one at 3 months and it was only repeated when endometrial thickness at 6 months was greater than 8 mm. During the followup period no other treatment or placebo was administered that might obscure the fibroid evolution or symptoms and thus any chance of a placebo effect as a possible explication of an improvement sustained in the prevalence of symptoms was eliminated. The main variable to

evaluate efficacy was the percentage change in fibroid volume at 6 months in M grp and 6 months after its termination.

Secondary variables used to estimate efficacy were percentage change in the fibroid volume, changes in prevalence of symptoms of the myoma, intensities were evaluated by asking the patient herself to categories symptom into mild,moderate and marked category. All these variables were measured in each of the study evaluation periods.The main variables to evaluate safety were the frequency of simple hyperplasia. Other variables to evaluate safety were changes in endometrial thickness measured by ultrasound (mm) an mifepristone side effects. The subjects were assigned to one or the other groups at **random** once the subject met inclusion criteria and exclusion criteria, informed consent was taken. In all cases $p < 0.05$ was considered significant and all tests were twotailed. Data were processed with the SPSS 11.5

OBSERVATIONS AND RESULT

Inclusion and adherence to the treatment

55 women of reproductive and perimenopausal age group with fibroid of varying sizes met all the eligibility criteria and consented during the allotted tenure. 30 cases were allotted in M group (mifepristone) and 25 cases were taken as control.

Mifepristone group: 8 cases dropped out of study,3 wanted surgical treatment during course of treatment,5 loss to follow up due to non availability of drug for variable period of time. cost factor was also there in all those who dropped out of study.In Control group none of the patient dropped out of study.

Most patients were between 2525 yrs (44.4% n=47)

Initial variables and comparison between treatment groups

Table below showsBaseline variables of subjects in treatment groups (values are presented as mean)

Baseline charecteristics	Mifepristone group(M) n=22	Control(C) n=25
Age (years)	36.22	34.68
BMI(kg/m2)	25.6	23.93
Fibroid volume(cm3)	**47.21** ±51.64	**68.36** ±126.18
Hemoglobin(g/dl)	10.83±1.45	10.84 ±2.11
Endometrial thickness(mm)	4.98±2.36	

One single myoma was present in 18/47 (38.29%), 18/ 47 (38.29%) subjects in the Control group and 50 mg mifepristone groups respectively (*P* = **0.730**). in control group 84 % fibroids were intramural, 8% were subserosal and 8 % submucosal while in mifepristone group 95% were intramural and 4.5% were subserosal. There was no significant differences between the two groups with respect to the distribution of the fibroids studied (*P* = 0.396). There was no significant differences between the two groups with respect to the distribution of the fibroids studied (*P* = 0.396) and for any of the general characteristics.

a) Efficacy of mifepristone group over control group: Efficacy evaluation was based on the 22 and 25 subjects in the mifepristone group and control group respectively, who completed treatment. 46.6% decrease (p=.007) and 67.43% (p<0.001) increase in mean myoma volume in mifepristone and control group respectively (p=0.008).

Table 2: below shows the changes in fibroid volume by mifepristone group and evaluation periods.

Evaluation at	n	Mean ±SD	95% CI of Mean
Baseline	22	47.21±51.64	
End of drug treatment(6mnths)	22	25.21 ±24.20	↓ 46.60%
6 months off drug treatment(followup)	16	29.58±28.88	↓37.34%

In Mifepristone group (50 mg daily for 6 months) at the end of the treatment there was **reduction** in size in 18/22 cases (**81.81%)** and **increase** in size in 4/22 cases(**18.18%).**

>90 % reduction in size seen in 7/18 cases(**38.88%**), out of which 4(**57.14%)** were**>4cm**.

There was a significant increase in average hemoglobin scores in the mifepristone group from pretreatment values to values on termination of treatment: 10.83±1.45 g/L to 11.8 ± .98 g/L (*P* = 0.001). In the control group, significant decrease in average hemoglobin scores from 10.84±2.11 to 8.22±1.16(<0.001).

Variable	Hb range Minmax	Group mifepristone
MeanHb (baseline)	8.213.6	10.83±1.45
Mean Hb (posttreatment)	9.913	11.82±0.98
P value		0.001(significant)

No significant change pre and post treatment was found in incidence of pain and dysmenorrhea among cases but there was significant reduction in incidence of menorrhagia in cases receiving mifepristone.(p<0.001).

Table below shows changes in symptom prevalence associated with the fibroid in mifepristone group at the beginning and end of treatment.

Variables	Pretreatment		Posttreatment		pvalue
	cases	%	cases	%	
pelvic_pain	5	22.7%	1	4.5%	0.185
Menorrhagia	11	50%	0	0	<0.001
Menstrual Irregularity	0	0	2	9.1%	0.488
Dysmenorrhea	3	13.6%	1	4.5%	0.606

B) Safety and side effect profile

Amenorrhea was not present in any case before treatment by mifepristone while 6 months into treatment 63.6% cases had amenorrhea in mifepristone groups (*P* , 0.001). 6 out of 14 cases were perimenopausal. None of the patient had significant side effect .Transient rise in AST/ALT was seen in 9.09% cases.

c) Endometrial biopsy

A pretreatment endometrial biopsy was performed on 19/22 subjects, with the diagnosis being secretory endometrium and proliferative endometrium. At the end of treatment 18/22 subjects were indicated for endometrial biopsy. .1/19 case underwent myomectomy and refused biopsy due to non improvement of symptoms, 3/22 case were unmarried but endometrial thickness was normal in post treatment follow up ultrasound so biopsy was not performed in unmarried cases.

10/18 subjects diagnosed with proliferative endometrium while, 7/18 had secretory endometrium while1/18 developed complex hyperplasia without atypia.

36.34 % increase in mean endometrial thickness seen following 6 months into the treatment by mifepristone.(p=0.036) increase was found to be statistically significant.

d) Analysis of follow up cases in Mifepristone group: 16 cases were followed up, no change noted in 12.5%. 68.75% reported increase in size, 9.09% was<2 cm, 72.72% were>4cm. >90% increase in size seen in 18.18% cases both were between 24 cm in size.

DISCUSSION

Leiomyomata contain both estrogen and progesterone receptors[1] and they are more in number in fibroids when compared with the myometrium.[2] Since leiomyoma has ovarian steroid dependency, we reasoned out that mifepristone may have an inhibitory effect on growth of leiomyomata. The etiology of uterine fibroids is not yet fully understood, but

several risk factors have been identified. The effects of mifepristone on uterine leiomyomata have been studied worldwide in several clinical trials; mifepristone can be compared with GnRH agonists in terms of efficiency.[3] dosage of mifepristone used in different clinical trials ranged from 5 to 50 mg and were either used solely to manage leiomyomata or used prior to surgery[4] to decrease the size. Ideal dosage effective for treatment of leiomyomata is sttill to be concluded. In a systematic review of six studies, it was found that mifepristone decreased the size of fibroid considerably and decreased the symptoms namely menorrhagia, dysmenorrhea, and pelvic pressure.[5]

In our study, we observed that treatment with mifepristone 50 mg daily for 6 months substantially decreased bleeding, size of fibroid and improved the symptoms markedly in symptomatic women. percentage reduction of fibroid volume is less than reference studies[6, 7] this may be due to difference in baseline myoma volume included in study. most of patients in present study has smaller volume compared to reference study ,so profound effect may be anticipated in larger fibroids.

The drug was well tolerated without any major side effects as evidenced by no dropouts. The effects of mifepristone in decreasing bleeding and size of fibroids are consistent with previous studies of the drug.[6] Previous trials suggested that maintenance of symptomatic improvement and reduction in leiomyoma volume was seen up to one year.[7] in our study size of fibroid reached almost its baseline size in 6 months follow up period but the symptomatic improvement was seen up to 6months off drug. Present study found significant rise(0.036) in mean endometrial thickness in cases, given the climate of mifepristoneinduced estrogen predominance. endometrial thickness was raised(>8 mm) in 4/22 patients(18%) but none of these patients were symptomatic our finding was in accordance with reference study.[8]

present study found raised transaminases in 9.09% cases which was transient and resolved spontaneously. this finding is consistent with reference study.[8] Nausea, vomiting, vague abdominal pain, headache, hot flushes, fatigue present minimum values as also found by above studies and are not worthy of mention in this study.

CONCLUSION

Mifepristone is effective in reducing size and symptoms associated with fibroid. Despite the fibroid reaching its pretreatment size there is still notable clinical improvement in both the

treatment groups. lack of reduction in follow up suggest that at present these drugs are not recommended as first line medical management of fibroid. The great effectiveness of these drugs along with the fact that they can be administered continuously or periodically, offers an alternative to many subjects like: Symptomatic perimenopausal women who awaits the onset of the menopause, Women who wants to postpone the surgery, Women who are unfit for the surgery at present. Further studies are required to determine whether benefits of the drug given for 6 months will be sustained if the drug is continued and so, it is yet to be determined for how long and whether any serious side effects emerge or not by its prolonged use.

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