

ROLE OF LOW DOSE MIFEPRISTONE IN THE TREATMENT OF SYMPTOMATIC FIBROID UTERUS: A DOUBLE CONTROL RANDOMIZED CONTROL TRIALRita Lal¹, Akriti Ashwini², Sweta Lal³**HOW TO CITE THIS ARTICLE:**

Rita Lal, Akriti Ashwini, Sweta Lal. "Role of Low Dose Mifepristone in the Treatment of Symptomatic Fibroid Uterus: A Double Control Randomized Control Trial". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 57, July 16; Page: 9990-10000, DOI: 10.14260/jemds/2015/1444

ABSTRACT: Fibroids are the most common benign tumors of the uterus primarily affecting the reproductive age group presenting with symptoms like menorrhagia, dysmenorrhea, pelvic pain and pressure symptoms and frequently infertility. Hysterectomy and myomectomy have been the surgical options for the management of symptomatic fibroids. Procedures like uterine artery embolization and thermal balloon ablation are expensive procedures and still not available in most centers. Various drug therapies like Gn RH analogues, danazol, etc. have been tried to reduce symptoms. The anti-progestin, mifepristone (RU 486) has been studied since the past few decades for its effect on reduction of symptoms of fibroid uterus. **AIMS:** The effect of low dose mifepristone given for three months was assessed on symptomatic fibroids over six months. **SETTINGS AND DESIGN:** This randomized control study here was done on 100 patients who presented with symptomatic fibroid to the department of obstetrics and gynecology at RIMS, Ranchi over a period of eighteen months. **MATERIAL AND METHODS:** The study group was given mifepristone 20 mg daily for three months and the control group was given a placebo. Both these groups were followed up for six months and assessment of symptoms like menorrhagia, dysmenorrhea, pelvic pain was done. Serial assessment of fibroid volume and uterine volume was done on ultrasound. **RESULTS AND CONCLUSION:** The data was analysed using chi square test. We found a significant decrease in the symptoms like severe menorrhagia, pelvic pain in the study group as compared to the control group. Also there was a significant reduction in size of the fibroid in the study group. Thus mifepristone was found to be effective in reducing symptoms caused by fibroid with minimal associated side effects.

KEYWORDS: Fibroid, Leiomyoma, Mifepristone, Antiprogestin.

INTRODUCTION: Fibroids are the most common benign tumor of the uterus primarily affecting the reproductive age group. The majority of fibroids remain asymptomatic. The classic symptom of fibroid is progressively increasing menorrhagia. Fibroids also cause dysmenorrhea, metrorrhagia, abdominal or pelvic pain, infertility and pressure symptoms like constipation, dysuria or retention of urine.

Small asymptomatic fibroids need only to be followed up from time to time. When symptomatic, the assessment of the appropriate treatment usually depends on the number of factors such as size and location of myomas, the intensity of symptoms, the age and the reproductive desires of the patient.

Surgical treatments like hysterectomy or myomectomy have for long remained the main treatment for leiomyoma. Though being definite mode of treatment, they are associated with anesthetic, operative and post-operative complications.

ORIGINAL ARTICLE

Many drugs have been used for medical therapy of fibroids. Most of the drugs like non-steroidal anti-inflammatory drugs, GnRH analogues, danazol have shown significant reduction in some symptoms but these drugs when stopped, symptoms can come recur. Levonorgestrel releasing intrauterine device reduces blood loss and uterine size. However this is not recommended when the uterine size is more than 12 weeks or there is distortion of uterine cavity. Recent studies have provided the evidence that progesterone has critical role in leiomyoma growth. This led to the introduction of antiprogestins for the treatment of fibroid.

The oral antiprogestin, mifepristone is fast emerging as an effective treatment for symptomatic fibroids. Mifepristone is a progesterone receptor antagonist blocks progesterone receptors in the fibroid and causes shrinkage. Mifepristone is a 19 norsteroid with antiprogestone and antiglucocorticoid activity. Mifepristone can be used before surgery to reduce the size of fibroid. Reduction in fibroid size technically simplifies the operative procedure. The decrease in leiomyoma volume and improvement in symptoms by mifepristone is comparable to GnRH analogues. Mifepristone has minimal side effects and is well tolerated. This study done in Rajendra Institute of Medical Sciences, Ranchi determines the effect of 20 mg of mifepristone on uterine size and fibroid volume, improvement in symptoms and its adverse effect on the patient.

MATERIAL AND METHODS: This study was on one hundred patients attending the department of obstetrics and gynecology, Rajendra Institute of Medical Sciences, Ranchi during the period from May 2012 to October 2013. Hundred patients with symptomatic fibroids were selected and randomly allocated into group I and group II.

Group I: Comprised of 50 patients to whom 20 mg of mifepristone was given daily for 3 months.

Group II: Comprised of 50 patients to whom placebo was given daily for 3 months.

Informed consent was taken from all patients, regarding the necessity of duration of treatment, the procedure and the possible adverse effects. Patients were followed for 6 months from the time of registration.

All the patients were screened on the basis of inclusion and exclusion criteria.

Inclusion Criteria:

1. Age > 18 yrs.
2. Complaint patient for follow up and required investigations.
3. Symptomatic fibroids.
4. USG shows total uterine volume > 160 cc with at least one fibroid > 2.5 cm in size.
5. Agree for non-hormonal method of contraception to prevent pregnancy.

Exclusion Criteria:

1. Patients with pelvic inflammatory disease, adenomyosis or endometriosis, suspected malignancy, abnormal uterine bleeding of any coagulopathy were excluded from the study.
2. Hb < 9 gm%.
3. Breast feeding mother or women planning pregnancy.
4. Patients with untreated abnormal pap smear.
5. Women on hormonal contraception or any other hormonal treatment in past three months.
6. Women with contraindication to use mifepristone like liver disease, kidney disease, severe respiratory disease or adrenal insufficiency.

ORIGINAL ARTICLE

A detailed history of each patient was taken and history of all presenting complains noted. Symptoms like dysmenorrhea, pelvic pain, menstrual blood loss, urinary and rectal symptoms were categorized and scored according to severity. Detailed menstrual history was taken. Obstetric history, past history, previous drug therapy, family history and personal history was recorded.

After a detailed history a thorough general and systemic examination was done and findings noted. Pelvic examination was done to rule out any cervical cause of bleeding. Bimanual examination was used to assess the size, position, consistency and mobility of the uterus and exclude out any other pathology.

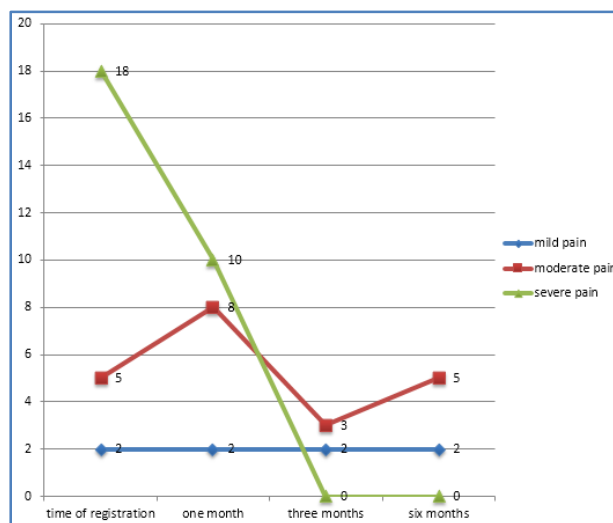
Routine Blood and urine investigations were done including thyroid function tests.

Pap smear was taken. USG was done in the department of Radiology, RIMS. Detailed ultrasound was done to assess the uterine volume, number of fibroids, fibroid volume any adnexal pathology and endometrial thickness. Ultrasound evaluation involved measurement of uterine volume and leiomyoma volume. Viscosmi formula was used for the uterine volume that is $\frac{4}{3} \pi W/2 \times L/2 \times T/2$ where W is uterine width on transverse section passing through the uterine fundus; L is the uterine length, measured on sagittal section from internal os to fundus, T is the uterine thickness measured on sagittal section between the anterior and posterior walls. Assessment of leiomyoma volume was done by the formula $\frac{4}{3} \pi abc$, where abc represent radii of the sphere in three dimensions. In case of multiple fibroids average volume of all leiomyoma was taken. Ultrasound was done at the time of registration, third month of therapy and at sixth month of follow up.

Also, endometrial aspiration was taken at the time of registration, then at three months of treatment and then after six months of therapy. It was done as a day care procedure using MVA cannula no 4 under paracervical block.

RESULTS: In this study of total 50 patients included in group I, there were 4 dropouts. All patients reported at 1st and 3rd follow-up visit. Four patients did not attend the follow up visit at six months. Among the 50 patients in-group II, there were 4 dropouts in the third month visit and six dropouts in the sixth month follow up visit.

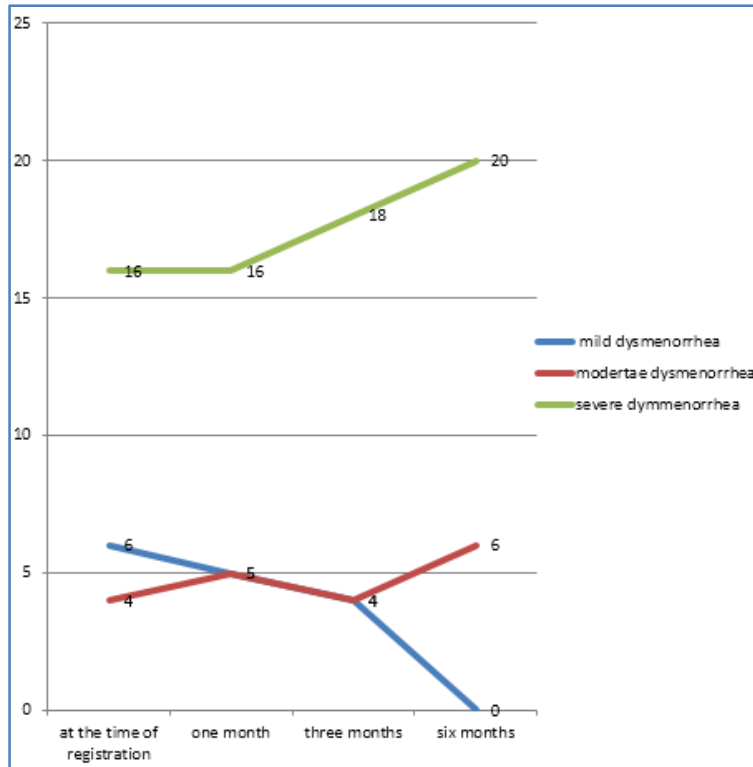
Graph 1: line graph showing intensity of dysmenorrhea in patients on mifepristone over 6 months follow up.



Graph 1

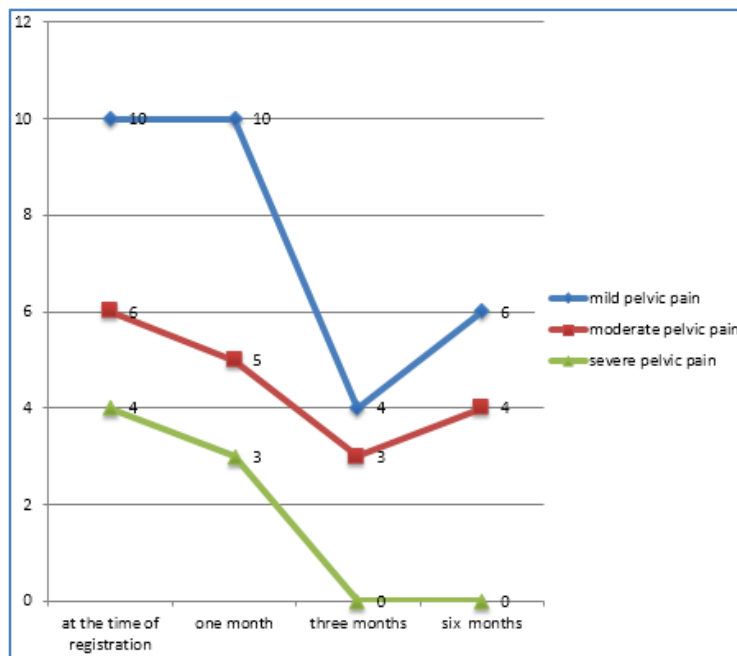
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Graph 2: line graph showing intensity of dysmenorrhea in patients on placebo over 6 months follow up.



Graph 2

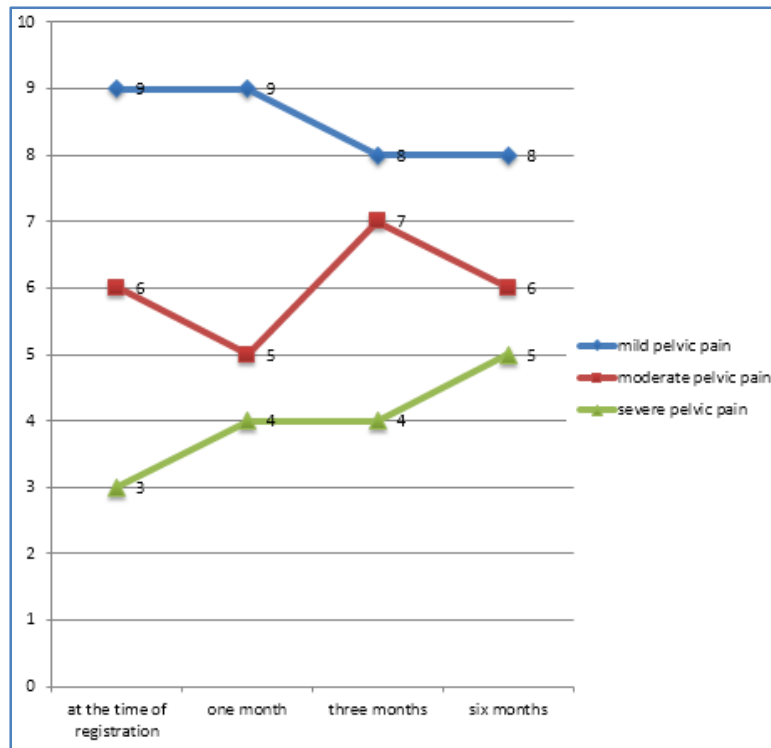
Graph 3: line graph showing intensity of pelvic pain in patients on mifepristone over 6 months follow up.



Graph 3

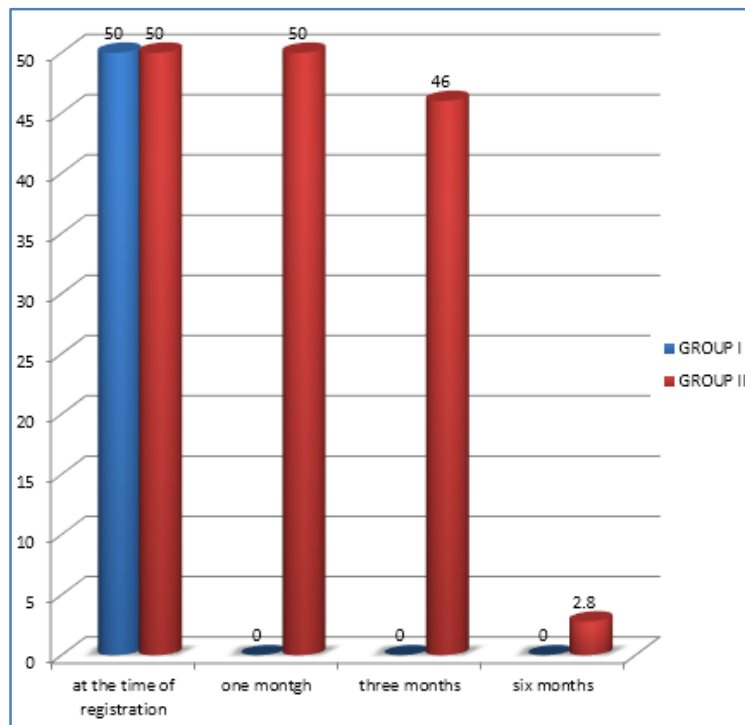
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Graph 4: line graph showing intensity of pelvic pain in patients on placebo over 6 months follow up.



Graph 4

Graph 5: bar graph showing decrease in menorrhagia in patients of both groups on follow up.



Graph 5

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Duration	Group I (Mifepristone)			Group II (Placebo)			P value
	Mean (cc)	SD	% change from baseline	Mean (cc)	SD	% change from baselline	
At the time of registration	256	18.83	-	260.94	17.82	-	>0.05
At one month	224.56	25.72	-12.28	263.38	17.45	+0.90	<0.001
At three months	187.02	23.63	-26.95	266.40	17.41	+2.09	<0.001
At six months	227.75	24.56	-11.13	269.96	17.86	+3.46	<0.001

Table 1: Table showing mean uterine volume(cc) during the study period

Duration	Group I (Mifepristone)			Group II (Placebo)			P value
	Mean (cc)	SD	% change from baseline	Mean (cc)	SD	% change from baselline	
At the time of registration	139.20	14.64	-	137.02	13.61	-	>0.05
At one month	119.52	13.25	-14.34	139.98	13.94	+2.16	<0.001
At three months	97.72	13.37	-29.80	143.52	13.80	+4.74	<0.001
At six months	104.42	14.21	-24.98	146.70	14.21	+7.06	<0.001

Table 2: Table showing mean fibroid volume(cc) during the study period

DISCUSSION: In the study most of the patients in both the groups were in the age group of 30-45 years with the mean age being 39.20 and 29.10 yrs in-group I and group II respectively. This was comparable to observation of Madhu Bagaria³ et al (mean age 40.3 yrs.) and Carbonell JL⁴ et al (mean age 39.6).

In the present study it was seen that the mean parity of patients in group I and group II was 2.34 and 2.70 respectively. This was comparable to the study done by Madhu Bagaria³ et al in which most patients were Para 3 or above.

In-group I, 50% of all patients had dysmenorrhea at the start of the study with 36% having severe dysmenorrhea. Eighty percent of these patients were completely relieved of their dysmenorrhea at three months and 72% had relief at six months too i.e. three months after stopping therapy. While in-group II there was a slight increase in number of patients with severe dysmenorrhea. Vidushi⁵ et al also found similar results with 25mg mifepristone daily for three months. They found that 77% and 71% of patients had complete relief from dysmenorrhea, at three months and six months of follow up, respectively.

Madhu Bagaria³ et al also found that 80% of patients were relieved completely of dysmenorrhea after three months of therapy with 10mg mifepristone.

Yang⁶ et al found 100% relief of symptom after three months with 10 and 20mg of mifepristone for 3 months.

ORIGINAL ARTICLE

In the present study in-group I, 60% of patients had complete relief from pelvic pain at three months and 50% had relief after six months. In group II there was slight increase in the number of patient with pelvic pain from the study to 6 months of follow up. Carbonell⁴ et al, Vidushi⁵ et al and Yang⁶ et al found most patients had relief of pelvic pain. Madhu Bagaria³ et al stated that there was relief of pelvic pain in only 33% of patients with 10 mg mifepristone daily for three months.

On comparing reduction in menstrual blood loss, 80% of patients of patient's in-group I developed amenorrhea; while none of the patients had any menorrhagia at the end of six months of study period, whereas in-group II menorrhagia persisted over the study period.

Madhu Bagaria³ et al and Vidushi⁵ et al found 84.2% and 90.4% patients developed amenorrhea with 10 mg mifepristone. The amenorrhea reverted back after a median of 34 days after stopping therapy. Carbonell⁴ et al found that 97% and 79% had complete relief from menorrhagia at three months of treatment and six months of follow up respectively. A study by Eisinger et al⁷ by prolonging the duration of therapy to six and 12 months, reported amenorrhea in 65% and 60% of patients respectively. This might indicate that as duration of treatment increases the prevalence of amenorrhea decreases. Thus from all these studies it can be concluded that mifepristone relieves heavy menstrual bleeding and improves the quality of life of patients.

In the study in-group I, 16% of patients had urinary symptoms and 4% patients had rectal symptoms at the start of study. All patients were relieved of their symptoms at the end of three months of therapy. At the end of six months only one patient of 50(2%) had urinary frequency. All the remaining 98% of patients had complete relief from their symptoms. While in group II (placebo) there was no relief in symptoms during the entire study period.

Carbonell⁴ et al in his study found that 91.4% and 77.14% patients got rid of their urinary symptoms at the end of three months and six months respectively on treatment with 5mg mifepristone. Rectal symptoms were relieved in 86.2% of patients with 2.5mg mifepristone and in 94.5% of patients with 5mg mifepristone for three months.

Esteve Carbonell JL⁸ et al in 2012 showed relief of symptoms in 75% and 74.8% patients after three months with 2.5mg and 5 mg mifepristone respectively.

When we analyzed the mean uterine volume, in group I, the mean uterine volume was 256cc at the time of start of the study which decreased by 12.28% after one month and 26.95% at the end of three months. At the end of six months the mean uterine volume was 227.75cc. The percentage decrease in mean uterine volume at the end of six months was 11.13% when compared with mean uterine volume at the start of the study. While in group II, mean uterine volume increased by 3.46% from baseline to the end of six months. Hence the difference in the results of two groups was statistically significant ($p < 0.001$).

Madhu Bagaria³ et al found 26.6% reduction in uterine volume after three months of therapy with 10 mg mifepristone. Yang⁶ et al found 33% reduction of uterine volume with 20mg mifepristone for three months. Eisinger et al⁹ found 48% and 49% reduction in uterine volume with 5mg and 10mg mifepristone respectively after six months of therapy.

Carbonell JL⁴ et al found that the percentage decrease in uterine volume, three months after therapy with 2.5mg and 5mg mifepristone was 18.2% AND 22.1% respectively. At three months of treatment follow up, the percentage reduction in uterine volume as compared to pretreatment follow up the percentage reduction in uterine volume as compared to pretreatment values was 8.1% and 11% with 2.5mg and 5mg mifepristone respectively.

ORIGINAL ARTICLE

All the studies discussed here shows that mifepristone had reduced the uterine volume but the results were slightly variable even with the same dose and also with the duration of treatment given.

In the present study in group I mean fibroid volume was 139.20cc at the time of registration which gradually decreased by 14.34% after one month and 29.80% after three months. At the end of six months the percentage decrease in fibroid volume as compared to pretreatment values was 24.98%. Whereas in group II the mean fibroid volume was 137.02cc at the start of the study which increased by 7.06% after six months.

The change in fibroid volume at the end of three months and six months in the two groups was statistically significant (<0.001)

Madhu Bagaria³ et al found 31% reduction in fibroid volume at three months with 10 mg mifepristone. Carbonell JL⁴ et al found in their study that the fibroid volume reduced by 27.9% and 15.4% after three months and six months respectively with 2.5mg mifepristone. The reduction in fibroid volume was by 46.4% and 28.6% after three months and six months respectively with 5mg mifepristone given daily for three months. Vidushi⁵ et al found that there was 35% reduction in fibroid volume after three months and 26.5% reduction in fibroid volume at six months with 2.5mg mifepristone given daily for three months. Eisinger et al⁹ found 49% decrease in fibroid volume at six months with 10mg mifepristone. Reinsch¹⁰ et al found reduction of 32% in fibroid volume with 25mg mifepristone. Yang⁶ et al found 33% decrease in fibroid volume with 20 mg mifepristone.

Most of the earlier studies with mifepristone have either taken uterine volume or leiomyoma volume as their study parameter. However studies with GnRH analogues have included both of these parameters in their study. Schlaff¹¹ et al using MRI imaging in this study have shown that GnRH analogues act more on the non myoma volume(42.7%) reduction than on the myoma volume reduction (30.4%). Hence this reduction in uterine volume is mainly due to its action on the non myoma volume. In the present study both these parameters were included and it was observed that the reduction in uterine volume (26.95%) is almost the same as the reduction in the fibroid volume (29.80%). This suggests that mifepristone reduces uterine volume by acting on leiomyoma and not on non myoma tissue.

There is increase in hemoglobin level from the time of start of study till the end of six months probably due to control of heavy menstrual bleeding. In group I the mean Hb at the time of registration was 9.6gm/dl which gradually increased and reached to 10.8gm/dl (Increased by 12.50%) at the end of three months. Even after discontinuing mifepristone the Hb levels was 10.17gm/dl (5.93%) more than pretreatment levels. At the same time in group II the mean Hb at the time of start of study was 10gm.dl, which gradually fell and became 8.66gm/dl at the end of six months. This was probably due to continued heavy menstrual flow in placebo group for six months. Madhu Bagaria ³et al found that there was a rise in Hb level from 9.5 to 11.2gm/dl from the baseline with mifepristone 10mg for three months. Vidushi⁵et al found there was an increase in Hb levels by 7.3% at the end of three months. The Hb levels at 6 months of follow up showed that it was maintained even after stopping treatment.

The side effects of mifepristone were very few such as nausea, vomiting, diarrhea, and hot flushes.

In the present study, among the patients who received mifepristone, 4% had nausea and 4% had hot flushes after one month. After three months of therapy, 8% patients complained of nausea and 8% had hot flushes.

ORIGINAL ARTICLE

The side effects disappeared on discontinuing the therapy. Reinsch¹⁰ et al found no incidence of hot flushes at 25mg mifepristone for three months, while Murphy¹² et al found 20% incidence of hot flushes at 25mg mifepristone for three months. Carbonell JL⁴ et al reported hot flushes in 9.4% and 15.6% of patients at some stage of study period when treated with 2.5mg and 5mg mifepristone respectively. Nausea was reported in 1.9% and 3.7% patients in 2.5mg and 5mg mifepristone receiving groups respectively. Madhu Bagaria³ et al found no incidence of side effects like nausea, fatigue, diarrhea and hot flushes in their study with 10 mg mifepristone for three months. Vidushi⁵ et al reported hot flushes in 7.1% and 6.8% of patients with 2.5mg and 5mg mifepristone respectively.

Thus the incidence of side effects with mifepristone is variable in the study groups even with similar doses.

A common concern in patients on mifepristone is rise in the serum SGPT levels. In the present study in group I, 4% of patients had raised SGPT levels (>40IU) at the end of three months. At the end of six months none of the patients had raised SGPT levels.

Though there was a rise in SGPT levels but all these patients had well tolerated the drug and all of them had SGPT level below 100 IU.

Reinsch¹⁰ et al and Yang⁶ et al found no incidence of raised SGPT in their study group. While Eisinger et al⁹ found 5% incidence of raised SGPT levels with 10mg mifepristone and 10% incidence with 5mg mifepristone.

Esteve Carbonell JL⁸ et al found that during the study period with 2.5mg and 5mg mifepristone, 5.6% patients in 2.5mg group and 8.1% patients in 5mg group, showed elevated liver transaminase levels.

The major concern with the used of mifepristone is endometrial hyperplasia. In this study, 34% of patients in group I showed endometrial hyperplasia at three months which reduced to none at the end of six months. None of them had atypical or complex hyperplasia. No patients in group II had endometrial hyperplasia during the study period. Eisinger et al⁹ showed 13.9% incidence of endometrial hyperplasia with 10mg mifepristone at six months and 4.8% at 12 months. Resumption of menses on prolonging the therapy might have been responsible for the regression of endometrial hyperplasia. Madhu Bagaria³ et al showed in their study that 63% of patients had endometrial hyperplasia with 10mg mifepristone. Carbonell JL⁴ et al studied that 2.5mg versus 5mg mifepristone in treatment of leiomyoma and that showed no incidence of simple endometrial hyperplasia at any time during the study period. None of the studies has reported any incidence of complex or atypical hyperplasia.

CONCLUSION: Uterine leiomyoma is one of the most frequent cause of menorrhagia leading to significant compromise in the quality of life in women mostly in their reproductive age group. Excessive vaginal bleeding, pain and pressure related discomforts have led women to opt for surgical procedures like myomectomy and hysterectomy. An effective and inexpensive medical management for this would be a great boon. Mifepristone can be useful in treating symptomatic fibroids. It can be a good alternative to GnRH analogues for use in pre-operative period. It can improve anemia and reduce the size of tumors to make surgery easier with lesser blood loss. Mifepristone can be a reasonable choice specially in perimenopausal women in whom myomas would regress after menopause and in unmarried patients who want to avoid surgery. Mifepristone is a well-studied anti progestin which has been use for various clinical indications. Its role in medical management of fibroid uterus has gained considerable interest over the past several years. The present study

ORIGINAL ARTICLE

treatment of fibroids with 20mg mifepristone shows that this treatment drastically and rapidly controls uterine bleeding. The most important and useful effect of mifepristone appears to be the control of excessive vaginal bleeding, leading to improvement in Hb levels. Hence mifepristone is effective in decreasing the severity of symptoms of leiomyoma and improving quality of life.

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ORIGINAL ARTICLE

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Date of Submission: 04/07/2015.
Date of Peer Review: 06/07/2015.
Date of Acceptance: 10/07/2015.
Date of Publishing: 15/07/2015.