EFFECT OF LOW DOSE MIFEPRISTONE IN SYMPTOMATIC UTERINE LEIOMYOMA

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ABSTRACT

BACKGROUND

Leiomyoma is the common benign tumour of uterus occurring in up to 20% of women with maximum incidence between 35-45 years of age leading to menorrhagia, pain and lump in abdomen. Medical treatment of leiomyoma are many with high cost and significant side effects. Mifepristone is a synthetic steroid with both anti-progesterone and anti-glucocorticoid activities.

AIM

The aim of the study was to evaluate the effect of 25 mg Mifepristone on uterine and myoma volume, haemoglobin and symptomatic improvement in cases of symptomatic leiomyoma.

MATERIALS AND METHODS

The present clinical study was conducted at a tertiary care centre at Visakhapatnam. This study was a prospective randomized double blind clinical trial. A total of 40 patients with symptomatic leiomyoma and normal endometrial histology were included in this study. After the written informed consent, symptoms like menorrhagia, dysmenorrhoea, pelvic pressure, low back ache was obtained. Severity of pain was graded according to visual analogue scale while quantification of blood loss was done using pictorial blood loss assessment chart (PBAC).

RESULTS

The mean age, parity and number of patients with symptoms was comparable in both the groups. After treatment, all the patients in group M had complete resolution of symptoms where as those patients in group C still continued to have the symptoms. After treatment, mean uterine volume in group M was 130.95±96.89 compared to that of 212.52±146.56 before treatment. The mean leiomyoma volume in group M, before treatment was 139.15±113.15 and after treatment was 78.15±71.18, a reduction of 43.84% was noted. In group C, the mean leiomyoma volume before treatment was 170.38±169.97 and after treatment was 177.78±171.56, an increase in volume of 4.34% was noted. The mean haemoglobin concentration in mifepristone group before treatment was 8.57±0.79 and after treatment was 10.09±0.99.

CONCLUSION

Low dose mifepristone is useful in case of symptomatic moderate sized leiomyoma, perimenopausal age group with symptomatic leiomyoma and high risk cases with uterine leiomyoma where surgery has been postponed. The clinical safety of the drug has yet to be determined by larger sample size with longer periods of treatment because of the associated risk of endometrial hyperplasia.

KEYWORDS

Mifepristone, Leiomyoma, Symptomatic, Evaluate, Effects.

HOW TO CITE THIS ARTICLE: Rani BS, Kumari PD, Usha P. Effect of low dose mifepristone in symptomatic uterine leiomyoma. J. Evid. Based Med. Healthc. 2016; 3(21), 909-913. DOI: 10.18410/jebmh/2016/206

INTRODUCTION: Uterine leiomyoma are commonest benign gynaecological tumours occurring in up to 25 per cent of women in reproductive age and about 40 per cent have symptoms severe enough to warrant therapy[1] Although the traditional concept supports a crucial role of oestrogen in promoting leiomyoma growth, recent evidence suggests that progesterone is essential for maintenance and growth of uterine leiomyoma and that oestrogen is required only for upregulation of progesterone receptors.[2]

Mifepristone is an antiprogestogen, a drug that blocks the effects of hormone progesterone. It reduces the size of the fibroid significantly. Since mifepristone doesn't suppress oestrogen levels as GnRH does, it was much better tolerated causing minimal hot flushes. The oldest, almost pure antiprogestin, mifepristone, has shown great effectiveness with different dosages in multiple studies into the treatment of this condition.[3,4] The present study was conducted to evaluate the effect of low dose mifepristone on leiomyoma related symptoms and size of leiomyoma.

Submission 13-02-2016, Peer Review 27-02-2016,
Acceptance 06-03-2016, Published 12-03-2016.
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DOI: 10.18410/jebmh/2016/206

MATERIALS AND METHODS: The present clinical study was conducted at tertiary care centre during the period of December 2008 to September 2010. This study was a prospective randomized double blind clinical trial. A total of 40 patients with symptomatic leiomyoma and normal endometrial histology were included in this study.

Inclusion Criteria:

1. Presence of leiomyoma in age group of 18–45 years, confirmed by clinical examination and transabdominal ultrasound.
2. History of leiomyoma related symptoms like menorrhagia, dysmenorrhoea, pelvic pressure, pelvic pain, backache.

Exclusion Criteria:

1. Presence of pregnancy or lactation.
2. Suspicion or documented evidence of ovarian, cervical or uterine malignancy.
3. History of hormonal treatment in past 3 months.
4. Histopathological evidence of endometrial hyperplasia.
5. Presence of liver, respiratory (asthma), renal, heart disease.
6. Presence of pelvic inflammatory disease
7. Presence of any other adnexal pathology
8. Patient necessitating early surgical intervention for uterine leiomyoma.
9. Patient on steroid usage.

After the written informed consent, history pertaining leiomyoma related symptoms like menorrhagia, dysmenorrhoea, pelvic pressure, low back ache was obtained. Severity of pain was graded according to visual analogue scale while quantification of blood loss was done using pictorial blood loss assessment chart (PBAC).

Before and after treatment, menstrual blood loss was assessed by asking patient how many tampons or towels used by them each day during menstruation and how they are stained (whether lightly or moderately or completely saturated with blood). We also recorded the number of clots passed and compare the size of clots.

All 40 patients were examined clinically and base line blood investigations (haemoglobin, liver function tests and renal function tests) were done. Trans abdominal ultrasound evaluation involved measurement of uterine volume, leiomyoma volume (largest leiomyoma volume). Viscosmi formula was used for uterine volume.

In case of multiple fibroids, volume of the largest leiomyoma was calculated. Endometrium was biopsied in premenstrual phase at the start of the therapy. Mifepristone 25 mg and placebo used in this study was calcium tablets. Patients in both the groups were followed monthly in premenstrual phase or on a fixed day of each month if they had amenorrhoea for a period of 3 months. Patients were enquired regarding their blood loss by Pictorial Blood Assessment Chart (PBAC) and leiomyoma related symptoms. Mean blood loss calculated at the end of treatment. Haemoglobin, liver function tests, kidney function tests were done. Side effects such as nausea, vomiting, diarrhoea, headache, fatigue, hot flushes and loss of libido were also made. After 3 months of treatment, trans abdominal ultra sound was done to assess uterine and leiomyoma volume. Endometrial biopsy was repeated on completion of therapy.

Unpaired t-test and chi square test were used to compare the base line parameters between the interventional and the placebo groups. Severity of symptoms between and within the groups, the percentage change in various symptoms score and ultrasound parameters at different time points were evaluated by using multiple measures ANOVA. If on comparison by multiple measures ANOVA the difference at different time points was found to be significant, the level of significance was determined by using the Tukey's test at 5% level of significance. P–value of <0.05 was taken as significant.

RESULTS: Following were the observations and results in the present study. The mean age and parity was comparable in both the groups. (Table 1). The number of patients with symptoms in both the groups before treatment was similar. After treatment at the end of 3 months, all the patients in group M had complete resolution of symptoms where as those patients in group C still continued to have the symptoms. (Table 2).

Age (In years)	Group M (n=20) (%)	Group C (n=20) (%)
18-27	5(25%)	6(30%)
28-36	6(30%)	7(35%)
37-45	9(45%)	7(35%)
Mean±SD	34.60±8.89	33.15±8.62
Parity		
Nulliparous	1(5%)	2(10%)
1	2(10%)	2(10%)
2	13(65%)	13(65%)
3	4(20%)	3(15%)

Table 1: Age and parity distribution (N=40)

Symptoms	Group M	Group C
Menorrhagia	15(75%)	14(70%)
Dysmenorrhoea	9(45%)	8(40%)
Pelvic Pain	1(5%)	0(0%)

Table 2: Symptoms in the two groups before treatment (N=40)

After treatment, mean uterine volume in group M was 130.95±96.89 compared to that of 212.52±146.56 before treatment. In group C mean uterine volume after treatment was 196.3±157.93, compared to that of 187.12±157.48 before treatment. The percentage change in mean uterine volume in mifepristone group was -38.38% (reduction in volume) and in group C was +4.91% (increase in volume). There was significant reduction in mean uterine volume in mifepristone group compared to that in control group.

Uterine volume has decreased in mifepristone group after treatment, when compared to that of before treatment, which is significant statistically p-value <0.05. Where as in control group there is a small increase in volume after treatment, compared to before treatment, which is not

statistically significant p-value >0.05. The increase in mean uterine volume might be due to slow growth of leiomyoma as it was left untreated in group C. Calcium has no effect on growth of uterine leiomyoma.

The mean leiomyoma volume in group M, before treatment is 139.15±113.15 and after treatment is 78.15±71.18, a reduction of 43.84% is noted. In group C, the mean leiomyoma volume before treatment is 170.38±169.97 and after treatment is 177.78±171.56, an increase in volume of 4.34% was noted. There was also a significant reduction in mean leiomyoma volume in mifepristone group compared to that of control group. Fibroid volume has decreased in mifepristone group after treatment, when compared to that of before treatment, which is significant statistically p-value <0.05. Where as in control group there is a small increase in volume after treatment compared to that of before treatment, which is not statistically significant p-value >0.05. (Table 3).

Uterine volume	**Group M**	**Group C**
Before Treatment	212.5206±146.56	187.1148±157.48
After Treatment	130.9515±96.84	196.3003±157.93
% Change	-38.38%	+4.91%
p-value	<0.05	>0.05
Leiomyoma (Fibroid) volume		
Before Treatment	139.1529±113.15	170.3764±169.97
After Treatment	78.1486±71.18	177.7757±171.56
% Change	-43.84%	+4.34%
p-value	<0.05	>0.05

Table 3: Comparison of uterine volume and fibroid volume in the two groups before and after treatment (N=40)

The mean haemoglobin concentration in mifepristone group before treatment is 8.57±0.79 and after treatment is 10.09±0.99. In control group the mean haemoglobin concentration before treatment is 9.44±1.11 and after treatment is 8.78±0.93. There was increase of haemoglobin concentration upto 17.74% in mifepristone group where as in control group there was a reduction in haemoglobin concentration upto 6.99%.

Haemoglobin concentration has improved in mifepristone group after treatment, when compared to that of before treatment, which is significant statistically p-value <0.05. Where as in control group there was a decrease in haemoglobin concentration after treatment, compared to before treatment, which was statistically significant (p-value <0.05). (Table 4)

Hb levels	**Group M**	**Group C**
Before	8.57±0.79	9.44±1.11
After	10.09±0.99	8.78±0.93
% Change	+17.74%	-6.99%
p-value	< 0.05	< 0.05

Table 4: Comparison of mean hemoglobin levels in the two groups before and after treatment (N=40)

All the patents in the group M had amenorrhoea whereas no patient attained amenorrhoea in group C. Hence menstrual blood loss index became zero in group M where as in group C there is a little increase in menstrual blood loss index. This difference is statistically significant. Only 6 patients in group M had fatigue. No other side effects were noted in both the groups. (Table 5).

	Group M	**Group C**
Before	150.75±30.14	157.5±31.77
After	0.00±0.0	164.00±32.02
% Change	100%	-4.1%
p-value	<0.05	>0.05

Table 5: Comparison of menstrual blood loss index (mean±sd, gm%) in the two groups before and after treatment (n=40)

DISCUSSION: The present study is to evaluate the effect of low dose mifepristone in the management of uterine fibroids. In the present double blind placebo controlled clinical trial, 25 mg mifepristone has been used. The drug was started from D1-D3 of cycle, that is, in the early follicular phase so that it starts acting before the development of dominant follicle. After treatment for 3 months, effect of drug was evaluated in terms of reduction of uterine volume and fibroid volume, side effects of the drug.

In the present study, the mean age was 34.60±8.89 and 33.15±8.62 years in mifepristone and control groups respectively. Mean age was comparable among the two groups. The mean age of mifepristone and control groups in the present study was similar to the studies of Madhu Bagaria, Amita Suneja et al.[5]

In the present study, in both the groups 13 patients (65%) had 2 children. Both the mifepristone and control groups were comparable in terms of parity. The parity wise distribution of mifepristone and control groups in the present study was similar to the studies of Madhu Bagaria, Amita Suneja et al.[5]

In the present study in group M, 10 patients had complaint of menorrhagia, 4 patients had complaint of dysmenorrhoea, 5 patients had complaint of both menorrhagia and dysmenorrhoea, 1 patient had pelvic pain. In group P, 12 patients had complaint of menorrhagia, 6 patients had complaints of dysmenorrhoea, 2 patients had complaints of both menorrhagia and dysmenorrhoea. Both groups are comparable in the symptomatology.

In study conducted by Madhu Bagaria, Amita Suneja et al,[5] mifepristone group had 12 patients showing menorrhagia, 5 patients dysmenorrhoea and 3 patients had pelvic pain. Where as in placebo group 11 patients had menorrhagia, 6 patients had dysmenorrhoea, 4 patients had both menorrhagia and dysmenorrhoea and 1 patient had pelvic pain.

In the present study amenorrhea was induced in 100% of patients in group M. Symptoms were relieved in 100% of patients in group M during treatment. In group P, symptoms continued during these three months of treatment.

In Madhu Bagaria, Amita Suneja et al[5] study amenorrhoea was induced in 85% of patients in mifepristone group. Reinsch et al[6] study showed 95% of patients had amenorrhoea in mifepristone group. Yen et al[7] study using 25mg of mifepristone showed 100% of patients had amenorrhoea.

Menstrual blood loss index in the present study was 150.75 before treatment compared to 0 after treatment in group M. In group P it was 157.5 before treatment compared to 164 after treatment. Menstrual blood loss index before and after treatment were comparable with that of Madhu Bagaria etal study.[5] (Table 6).

	Mifepristone group		**Control group**	
	Before treatment	**At the end of treatment**	**Before treatment**	**At the end of treatment**
Present study	150.75±30.14	0.00±0.0	157.5±31.77	164.00±32.02
Madhu Bagaria study	188.8	9.8	167	166

Table 6: Comparison of Menstrual blood loss index with other studies

Mean uterine volume in group M in present study is -38.3%. Where as in Madhu Bagaria, Amita Suneja et al[5] study it was -26.6%. Mean leiomyoma volume in group M in present study is -43.84%. Where as in Madhu Bagaria, Amita Suneja et al[5] study it was -30.2%. (Table 7). In Reinsch et al[6] found reduction of 32% in fibroid volume with 25 mg mifepristone. Yang et al[7] found 33% decrease in fibroid volume with 20 mg mifepristone.

Uterine volume	**Mifepristone group**		**Control group**	
	Before treatment	After treatment	Before treatment	After treatment
Present study	212.5206±146.56	130.9515±96.84	187.1148±157.48	196.3003±157.93
Madhu Bagaria study	256.2±235.6	188.0±203.5	281.6±417.5	281.1±417.2
Leiomyoma volume	**Mifepristone group**		**Control group**	
	Before treatment	After treatment	Before treatment	After treatment
Present study	139.1529±113.15	78.1486±71.18	170.3764±169.97	177.7757±171.56
Madhu Bagaria study	137±217.8	95.8±181	117.7±243.4	118.3±243.4

Table 7: Comparison of Mean uterine volume and Mean Leiomyoma volume with other studies

In present study % change in the haemoglobin in group M is +17.74.3% and in group P is -6.99%. Where as in Madhu Bagaria, Amita Suneja et al[5] study it was +16% in mefiprestone group and -2% in control group.

Before treatment in both the groups all patients had normal endometrial histopathology as patients with abnormal endometrial histopathology (hyperplasia, atypical hyperplasia) were excluded from the study. After treatment also, patients in both the groups in present study had normal endometrial histopathology. These results were comparable with that of Reins ch etal study.[6] No cases of endometrial hyperplasia noted in this study.

In Madhu Bagaria, Amita Suneja et al[5] study 4.8% of patients in mifepristone group had simple endometrial hyperplasia. It is noteworthy that in this study, all the patients with endometrial hyperplasia showed normal endometrium on histopathology specimens when they underwent surgical intervention in the form of hysterectomies and D&C. This indicates that the drug induced endometrial changes were reversible.

No significant side effects were noted in both the groups. Only 6 patients in group M had fatigue. Even though not included in the present study, patients were followed up for 6 months after 3 months of treatment. In group M, patients have resumed their menstrual cycle after stopping mifepristone and had no recurrence of symptoms till now.

Vidushi Kulshrestra et al[8] in their study compared the impact of low dose mifepristone (10 mg and 25 mg) respectively. Mifepristone (10 and 25 mg) caused symptomatic relief with more than 90 per cent reduction in menstrual blood. Greater myoma size reduction occurred with 25 mg dose. Amenorrhoea was developed in 90-95 per cent patients which was reversible. It can be a reasonable choice for management of uterine leiomyoma as it is administered orally, cost-effective and has mild side effects. Repeat endometrial-histopathology did not reveal any complex hyperplasia or atypia in either group.

Engman M et al[9] used 50 mg Mifepristone and his observations were, there was significant decrease in the total leiomyoma volume, bleeding days and increase in serum hemoglobin values. Endometrial biopsies showed no premalignant changes or changes in mitotic indices.

Fiscella K et al[10] used 5 mg mifepristone, showed an improvement in leiomyoma-specific quality of life. Forty-one percent became amenorrhoeic, rates of anaemia improved, and adjusted uterine size was reduced by 47%. Compared with the placebo group, improvements in these outcomes in the treatment group were significantly greater (P<.05 to .001). There were no significant differences in adverse effects between the groups. No Adverse effects and endometrial hyperplasia was noted in any participant.

Shika Seth et al[11] analysed ninety-three perimenopausal women of age 35-50 years having symptomatic myoma after administering 25 mg Mifepristone for three months. Her observational were Mean uterine volume reduced to 63.69% of baseline, mean dominant Myoma volume reduced to 53.62% and hemoglobin level raised to 137% after complete three months of treatment. Changes persisted in next three months' post-treatment follow-up, while hysterectomy was required in 10(12.2%) cases.

CONCLUSION: From the present study it can be concluded that: There was relief of leiomyoma related symptoms with low dose mifepristone. There was significant reduction of mean uterine volume and mean leiomyoma volume with low dose mifepristone. There were neither significant side effects nor increased incidence of endometrial hyperplasia with low dose mifepristone. Incidence of endometrial hyperplasia is dose dependent which is seen with high doses. Three months' therapy of 25 mg mifepristone is efficacious & acceptable for the treatment of symptomatic leiomyoma. Low dose mifepristone is more useful in case of symptomatic moderate sized leiomyoma, perimenopausal age group with symptomatic leiomyoma and high risk cases with uterine leiomyoma where surgery has been postponed. Low dose mifepristone can avoid blood transfusion and hysterectomy in a lot of symptomatic myoma cases. The clinical safety of the drug has yet to be determined by larger sample size with longer periods of treatment because of the associated risk of endometrial hyperplasia.

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