Effect of Mifepristone on Uterine Fibroid with special reference to Symptoms and its Size

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Abstract: *Uterine Fibroids are most common growth of female reproductive tract in premenopausal women. Non surgical treatment options for this have limitations. So this Prospective interventional study was conducted to evaluate the effect of low dose Mifepristone treatment for 3 months on fibroid size and related symptom.*

Patients: *Twenty five patients with symptomatic fibroid, aged 20-50 years.*

Intervention: *Patients received 10mg Mifepristone daily for 3 months*

Method: *Baseline data regarding fibroid volume, Hb value, PBAC (Pictorial Blood Assessment Chart) & VAS (Visual analogue Scheme) score were recorded and these data regarding above parametres again collected at the end of 1st month & 3rd months of therapy.*

Results: *Mifepristone treatment significantly reduced fibroid mean volume from 91.13cm^3 at enrollment to 38.73cm^3 after 3months of treatment. Mean PBAC score was reduced for 111.52 at enrollment to 2.36 at the end of 3rd month of therapy. At 3 months 22 of 25 case (88%) developed amenorrhoea. At the end of therapy hemoglobin mean value was raised by 2.38 gm/dL from the baseline mean value of 8.70mg./dL. There were no major side effects during the course of the study and treatment was well tolerated.*

Conclusion: *Low dose Mifepristone (10mg) reduces fibroid size and related symptoms with no side effects among women with symptomatic fibroids.*

Key Words: Mifepristone, Leiomyoma, Fibroid Volum, Menorragia and Amenorrhoea

I. INTRODUCTION

Uterine leiomyoma are commonest benign gynaecological tumours occurring in up to 25 percent of women in reproductive age and about 40 percent have symptoms severe enough to warrant therapy[1], with peak incidence of symptoms occurring in women in their 30s and 40s.

Uterine fibroids are most common growth of female reproductive tract, 2-3 times more common in Afro-Carribbean women. Definitive treatment for symptomatic myomas has always been surgical and myomas accounts for 40 percent of all hysterectomies in premenopausal women[2].

Non surgical treatment options for symptomatic myomas have limitations. Danazol reduces uterine volume by 18-23 percent, but is associated with marked androgenic side effects. Gonadotropin releasing hormone agonist reduces leiomyoma size to about 50 percent in three months but is expensive, has to be given parenterally and is also associated with hypoestrogenism leading to hot flushes, vaginal dryness

and bone loss[3]. Cessation of GnRH causes regrowth of myoma and recurrence of symptoms. Uterine Artery Embolization has been shown to reduce leiomyoma size by 35-69 percent, but there are potential risks of premature ovarian failure and uterine synechia.

Mifepristone (RU 486) is a progesterone receptor modulator with primarily antagonistic properties. It binds strongly to endometrial progesterone receptors, minimally to oestrogen receptors and up regulates androgen receptors[4].

It is a well studied antiprogestin, which has been in use for over two decades for various clinical indications.[5,6] Effect of Mifepristone on follicular development, ovulation, endometrial development and function is dependent on dose and timing of exposure[7].

So this study was studied to evaluate effect of low doses Mifepristone on uterine fibroid with special reference to symptoms and its size.

II. METHODOLOGY

This hospital based intervention study was conducted in Department of Obstetrics and Gynecology, Sardar Patel Medical College, Bikaner during study period of one year from 2014 to 2015.

All symptomatic cases of fibroid between 20-50 years of age with uterine fibroid more than 5cm on USG were included in this study. Patients with uterus size more than 20 weeks, Fibroids more than 15cm by USG, Renal or Hepatic dysfunctions, Suspected adenomyosis, Current genital infection and Endometrial hyperplasia with atypia and use of hormonal medication (Progestogens / GnRH) within 3 months were excluded from study. Patients who has not completed 3 months treatment were also excluded from study.

After approval from Institutional Research Board study was started and was done on finally recruited eligible 25 subjects from August 2014 to September 2015. After taking Informed written consent demographic and baseline clinical profile including details of menstrual cycle, symptoms and their severity was noted. According to WHO criteria hemoglobin less than 12gm/dL was taken as anemia (mild: 11.9-10gm/dL, moderate 10-7gm/dL, severe <7gm/dL). Menstrual blood loss was assessed by pictorial blood loss assessment chart (PBAC) scores[4], which is a semi-quantitative assessment that takes into account number of pads soaked, their degree of soakage, passage of clots and episodes of flooding. A score of 100 or more accounts to menorrhagia.

Visual analog scale (VAS) score was noted for pain, dysmenorrhoea, dyspareunia, pelvic pain and pressure symptoms, where patients were asked to describe their pain on a scale of 0 to 10, before and after the treatment, with “no pain” taken at zero and “worst possible pain” at 100.

A complete general and gynaecological examination was done. Blood testing was done for hemoglobin, liver and kidney function tests. Ultrasound was done to confirm the diagnosis of leiomyomas as well as to ascertain number, site, volume of myomas and to rule out any other pelvic pathology. Volume of each myoma was calculated and added in cases with multiple myomas. Fibroid volume was calculated by the ellipsoid method and the formula V=0.5233(D1xD2xD3) was used, where D1, D2 and D3 are the longitudinal, transverse and cross-sectional diameters (in cm) of the fibroid, respectively. In multiple myomas, volumes of all myomas were added. Endometrial aspiration was performed to rule out any abnormal histopathology at the time of recruitment.

After recording all baseline data, Mifepristone was given as 10mg/day, starting initially from day 2nd - 3rd of period. Treatment was given for 3 months and patients were followed up at 1 & 3 months while on therapy. Again the supra said variables related to symptoms and fibroid size were recorded at every follow ups i.e. 1 & 3 months.

Since Mifepristone is available in India for induction of medical abortion as 200mg tablet, capsules of 10mg was prepared from 200mg tablet in Pharmacology department by crushing tablets in powder form, and then filling the capsules according to the weight.

Data thus collected were compared from their initial visit two of every follow ups i.e. 1 & 3 months. Significance of difference in proportion was by Mann Witteny test and significance to difference in mean size was inferred by Paired't' test and repeated ANOVA and Dunnel test.

III. RESULTS

3.1 Description of Study Population

Total of 25 patients were recruits and followed up at Gynecology outpatient department & all of them completed three months treatment duration. Majority of the cases were in age group of 30-40 years with mean age 37.16 years with mean BMI 26.64 Kg/m2. Mean parity was 2.88. Mean duration of symptoms was 12.28 months with PBAC scores 111.52, VAS score 6.24, Fibroid volume 91.13 cm^3. Mean Hemoglobin level was 8.7 gm/dL. (Table 1).

Table 1
Baseline Characteristics of Participants

Baseline Characteristics of Participants	Mean	SD
Age (in year)	27.16	5.54
BMI (Kg/m2)	26.64	1.99
Parity	2.88	1.48
Duration of Symptoms (in month)	12.28	9.52
PBAC Score	111.52	36.86
VAS Score	6.24	0.93
Fibroid volume (cm^3)	91.13	87.74
Hemoglobin (gm/dL)	8.70	0.37

Out of total 25 patients, in 1st visit **e**xcessive vaginal bleeding was reported by 21 (84%) cases, followed by backache & pain abdomen by 72% & 52% cases respectively. After Mifepristone although all the studied symptoms were observed in lesser number of cases after 3 months treatment but it was found significant only in maenorragia and backache. (Table 2)

Table 2
Comparison of Pain Related Symptoms at First visit and three months after Mifepristone

Pain Related Symptoms	At Ist Visit		After 3 month of treatment		P value LS
	No. of Patients	(%)	No. of Patients	(%)	
Meanorragia	21	84	12	48	0.017 **S**
Backache	18	72	5	20	0.043 **S**
Dysmenorrhoea	7	28	2	8	0.239 NS
Pain Lower Abdomen	13	52	5	20	0.177 NS
Heaviness at Lower Abdomen	4	16	1	4	0.417 NS
Dyspareunia	2	8	1	4	0.973 NS

Mean baseline fibroid volume was 91.13 (30.77-432.70) cm^3 at the time of recruitment. Although this mean fibroid volume was decrease at the end of the 1st month also from 91.13 to 66.48 cm^3 but it was not significant but when this crease from baseline to end of third month (from 91.13 to 37.73 cm^3 it was significantly decreased. (Table 3).

Table 3
Comparison of Fibroid Volume at First visit and Follow ups after Mifepristone

Fibroid Volume (in cm^3)	At 1st Visit		At 1st Month		At 3rd Month	
	No. of Patients	(%)	No. of Patients	(%)	No. of Patients	(%)
≤50	10	40	13	52	19	76
51-100	9	36	9	36	5	20
101-150	2	8	2	8	1	4
151-200	2	8	0	0	0	0
201-250	1	4	0	0	0	0
>250	1	4	1	4	0	0
Mean ± SD	**91.13 ± 87.74**		**66.48 ± 70.43**		**37.73 ± 30.55**	

ANOVA = 3.94 P Value =0.024 LS =S

--- Multiple Comparisons - Dunnett ---

Comparison	Difference of means		SE	p	q'	**P<.05**
1 vs 3:	37.73 -	91.13 = -53.4	19.04	3	2.805	**Yes**
1 vs 2:	66.48 -	91.13 = -24.65	19.04	3	1.295	**No**

Degrees of freedom: 72

In this study mean baseline mean PBAC at the time of enrollment was 111.52 (29-170). This mean PBAC score significantly decreased not only after 3 months of treatment but also after one month treatment from 111.52 to 3.04 in 1st month and from 111.52 to 2.36 in 3 months. (Table 4)

Table 4
Comparison of PBAC Score at First visit and Follow ups after Mifepristone

PBAC Score	At Ist Visit		At Ist Month		At 3rd Month	
	No. of Patients	(%)	No. of Patients	(%)	No. of Patients	(%)
≤ 50	3	12	25	100	25	100
51-100	1	4	0	0	0	0
101-150	18	72	0	0	0	0
151-200	3	12	0	0	0	0
Mean ±SD	**111.52 ± 36.85**		**3.04 ± 8.55**		**2.36±6.89**	

ANOVA = 200.24 P Value <0.001 LS =S

--- Multiple Comparisons - Dunnett ---

Comparison	Difference of means			SE	p	q'	P<.05
1 vs 3:	2.36 -	111.5 =	-109.2	6.279	3	17.385	**Yes**
1 vs 2:	3.04 -	111.5 =	-108.5	6.279	3	17.276	**Yes**

Degrees of freedom: 72

Mean baseline VAS scores at the time of enrollment was 6.24±0.93. Like PBAC scores, this mean VAS score significantly decreased not only after 3 months of treatment but also after one month treatment from 6.24 to 2.28 in 1st month and from 6.24 to 1.18 in 3 months. (Table 5)

Table 5
Comparison of cases according to VAS Score (N=25)

VAS Score	At 1st Visit		At 1st Month		At 3rd Month	
	No. of Patients	(%)	No. of Patients	(%)	No. of Patients	(%)
No Pain (0)	0	0	1	4	3	12
Mild Pain (1-3)	0	0	20	80	22	88
Moderate Pain (4-6)	15	60	4	16	0	0
Severe Pain (7-10)	10	40	0	0	0	0
Mean ±SD	**6.24 ±0.93**		**2.28 ± 1.14**		**1.28 ± 0.74**	

ANOVA = 190.27 P Value <0.001 LS =S

--- Multiple Comparisons - Dunnett ---

Comparison	Difference of means			SE	p	q'	P<.05
1 vs 3:	1.28 -	6.24 =	-4.96	0.2689	3	18.444	**Yes**
1 vs 2:	2.28 -	6.24 =	-3.96	0.2689	3	14.725	**Yes**

Degrees of freedom: 72

The mean Hemoglobin value of the cases at the time of recruitment in the study was 8.70±0.37 gm/dL. It was increased to 11.08±0.42gm/dL at the end of 3rd month of the therapy ($p<0.0001$).

Liver enzyme were not affected after 3 month of Mifepristone therapy showing Mifepristone does not have any adverse effect on liver function on short term use for fibroid treatment. No serious adverse effect of drug was noted, however hot flushes, fatigue & headache each of the side effect was reported by one case (4%) due to antagonistic effect of RU486.

IV. DISCUSSION

Uterine fibroids are very common non-cancerous (benign) growths that develop in the muscular wall of the uterus. While fibroids do not always cause symptoms, their size and location can lead to problems for some women, including pain and heavy bleeding.

The initiation and growth of myomas likely involves a multistep cascade of separate tumour initiators and promotors. Although the initiators of somatic mutations remain unclear, mitogenic effect of progesterone may enhance propagation of somatic mutations. Oestrogen and progesterone appear equally important as promotors of myoma growth.

While there are no agents that could be described as definitive stand-alone treatments for fibroid disease, there is a wide range of agents that are used in aspects of management of this common tumour. Gonadotropin releasing hormone agonist, selective oestrogen receptor modulators (SERMs), antiprogestins (RU486 and asnoprisinil), aromatase inhibitors, carbegoline, danazol and gestrinone are potential agents that have been used to varying degrees. Increasing knowledge of biology of uterine fibroids is stimulating development of newer non-hormonal therapies.

In this present prospective study 10mg dose of Mifepristone has been used, as per the result of previous studies, 10mg of Mifepristone was as effective as high doses (25mg & 50mg) with fewer side effects. V. Kulshreshtha et al[8] 2013 studied that 10mg RU486 is as effective as 25mg RU486 for treatment of uterine fibroid.

In our study, majority of cases were in age group of 30-40 years, which correlates well with age group most commonly found having fibroids and related problems. In this study mean BMI of patients was 26.64kg/m^2, which shows that fibroids are more common in overweight and obese patients. The higher mean BMI is reflecting hyper estrogenic state of participants. Due to availability of limited data about safety & efficacy of this drug, regarding future pregnancy, we did not included nulliparous & infertile women in our study.

Excessive Vaginal bleeding was main problem for women, compelling them to visit health care facilities, as it affected their day to day activities; health status & work efficiency. This symptom was reported by 82% cases, followed by backache & pain abdomen by 72% & 52% cases, respectively.

The fibroid volume was reduced by 27% and 58% at the end of 1st month and 3rd month, respectively. Fibroid volume reduced significantly from baseline to the end of treatment ($p<0.006$). Though 1 of 25 cases showed enlargement in fibroid size during therapy however, she got enough relief in symptoms (both bleeding & pain).

Both Oestrogen Receptor and Progesterone Receptor are more abundant in leiomyoma cells than in adjacent myometrium, suggesting that myomas are sex-steroid dependent tumours. Oestradiol & progesterone seem to stimulate myoma cells growth either directly or through mediation of growth factors. Progesterone also promotes myoma growth by inhibiting apoptosis of leiomyoma cells. Direct effect in reducing number of progesterone receptors, might be a mechanism of reduction of size of fibroid by mifepristone.

The similar results were obtained by Shikha Seth et al[9]. She observed 53.62% reduction in volume of dominate fibroid. Percentage decrease in size of fibroid in studies done by Murphy AA et al[10] (in 25mg Mifepristone group), Joseph Lluis et al[11] and Eisinger et al[12] (in 10mg mifeprisotne group) was 56%, 57% & 49%, respectively, which are comparable to our study. Sinha M. et al[13] observed 80% reduction in fibroid volume which was higher than our study.

The amount of bleeding was recorded using PBAC scoring system during all 3 visits & comparisons of results were made. PBAC score was reduced by 97% & 98% at end of 1st month and 3rd month, respectively. Reduction in PBAC score was significant from baseline to at end of treatment ($p<0.0001$) & effect started from the first follow-up. This is due to suppressive effect of RU486 on endometrial and vasculature by acting on VEGF. Twenty two cases (88%) became amenorrhoeic at the end of treatment. Probable hypothesis for amenorrhoea is that Mifepristone delays or inhibit ovulation.

In this study conducted by V. Kulshreshtha et al[8], PBAC score was reduced to 92.4% and 96.4% while, 95.7% and 90.4% of patients developed amenorrhoea in 10mg and 25mg Mifepristone group, respectively. These results are comparable to our study.

The patients were followed for 3 month for amount of pain felt, on a pain analogue scale. There was 63% & 79% reduction in pain score at end of 1st month & 3rd month of therapy, respectively, in our study. Backache was reported by 72% of patients at start, which reduced to 20% at the end of therapy (P value <0.043). There was a significant reduction in complain of backache at the end of therapy. Improvement in other pain related symptoms were not significant, however severity of pain symptoms were decreased significantly ($P<0.001$).

In our study hemoglobin value was raised by 8.6% & 27% at the end of 1st month and 3rd month of treatment, respectively. Improvement in hemoglobin value was significant in our study (p value 0.0001). At the end of therapy hemoglobin value was raised by 2.38 gm/dL from the baseline value of 8.70 gm/dL. Similar results were noticed by Shikha Seth et al[9], She observed that Hb values were raised by 2.8 gm/dL at the end of therapy.

Although this study had few methodological problems i.e. no long term follow up period and small sample size. However, results have shown that Mifepristone caused significant reduction in fibroid size and alleviated fibroid related symptoms. Further studies are needed to determine that how long the benefits of drug will sustain after discontinuation of treatment and what would be the adverse effects of drug if it is used for a prolonged period. Treatment was well tolerated by all participants as evidenced by adherence of patients to treatment & minimal side effects.

Table 6
Comparison of present study with main Clinical Studies on Mifepristone for Uterine Myomas

Studies	No. of Patients	Mifepristone dose (mg/day) Orally	Duration of treatment (moths)	Reduction in Fibroid Volume (%)
Present Study	25	10	3	58
Murphy et al 1995[10]	9	5	3	26
Murphy et al 1995[10]	11	25	3	56
Eisinger et al 2003[12]	16	5	6	48
Eisinger et al 2003[12]	16	10	6	49
Fiscella and colleagues 2006[14]	22	5	6	40
Joseph Lluis et al 2008[11]	50	5	3	57
Joseph Lluis et al 2008[11]	50	10	3	45
M. Engman et al (2009)[16]	15	50	3	34
Sucheta Mukharji et al2011[17]	30	25	6	160 ml
V. Kulshreshta et al 2013[8]	70	10	3	36
V. Kulshreshta et al 2013[8]	73	25	3	22
Sinha M et al(2013)[13]	50	25	3	80
Shikha Seth et al (2013)[9]	93	25	3	46

V. CONCLUSION

Low dose Mifepristone showed a speedy & better control of bleeding and alleviation of pain related symptoms that improved general condition of women, relieved their anxiety, provided them a sense of well being with few ignorable side effects.

Mifepristone can be used for temporary relief of symptoms for short periods. This application is suitable in women with symptomatic fibroids in perimenopausal years or in patients not suitable for surgery due to medical reasons.

CONFLICT

None declared till date.

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