|| Print ISSN: 2589-7837 || Online ISSN: 2581-3935 ||
International Journal of Medical Science and Diagnosis Research (IJMSDR)
Available Online at www.ijmsdr.com
Volume 3, Issue 1; January: 2019; Page No. 153-157

ROLE OF MIFEPRISTONE (10MG) IN TREATMENT OF UTERINE MYOMA

[1]lata Rajoria, [2]Sarita Agarwal, [3]Rajni Bansal, [4]Neelam Bharadwaj, [5]Pawan Agarwal

[1]Obstetrics and Gynecology Sr. Professor, SMS MC and RUHS, Jaipur and India

[2]Obstetrics and Gynecology and 3rd yr Post Graduate Student, SMS MC and RUHS, Jaipur and India

[3]Obstetrics and Gynecology and 3rd yr Post Graduate Student, SMS MC and RUHS, Jaipur and India

[4]Obstetrics and Gynecology and Sr. Professor, SMS MC and RUHS, Jaipur and India

[5]Obstetrics and Gynecology and Assistant Professor, SMS MC and RUHS, Jaipur and India

Conflicts of Interest: Nil

ABSTRACT:

Objectives: To evaluate the effect of low-dose mifepristone (10 mg) on symptomatic uterine myoma

Study design: Prospective observational study

Materials and methods: hundred women of age 20 to 45 years having symptomatic myoma were selected from gynecology outpatient department and given 10 mg mifepristone once daily continuously for 3 months. Baseline myoma size, volume, their number, position, characteristics, hemoglobin and blood parameters, were taken and Total duration of the treatment was 3 months. Follow-up made at 1st, 3rd and 6th month (3 month after stopping the treatment). At each follow-up improvement in symptoms, PBAC score, VAS score, fibroid size, haemoglobin changes were recorded.

Statistical analysis: Done by calculating mean, standard deviation, standard error and percentage distribution of variables.

Results: Menorrhagia was the commonest symptom for which patients report to hospital. Mean dominant myoma volume reduced from 62.89 ± 34.69 to 45.34 ± 28.43 (30.11 ± 5.21%) at 3 months and hemoglobin level raised to 19.57% after complete treatment of 3 months. Changes persisted in next 3 months post-treatment follow-up, while hysterectomy was required in 11(11.0%) cases.

Conclusion: Three months treatment of 10 mg mifepristone effectively controls bleeding, reduce myoma volume, improve haemoglobin and reduced hysterectomy in symptomatic myoma cases.

Keywords: Mifepristone, Myoma, Medical treatment, Antiprogesterone.

1. Introduction

Uterine myoma are the 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.

The definitive treatment for symptomatic myomas has always been surgical and myomas accounts for 40 percent of all hysterectomies in premenopausal women[2]. Surgical treatment can not be recommended to women not in advanced age and those who want to preserve their uterus.[3] 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

Corresponding author: Sarita Agarwal

parenterally and is also associated with hypoestrogenism leading to hot flushes, vaginal dryness and bone loss[4]. Cessation of GnRH causes regrowth of myoma and recurrence of symptoms. Recent evidence suggests that progesterone is essential for maintenance and growth of uterine leiomyoma and that oestrogen is required only for up regulation of progesterone receptors.[5]Mifepristone (RU 486) is a progesterone receptor modulator with primarily antagonistic properties. It binds strongly to endometrial progesterone receptors, minimally to estrogen receptors and upregulates androgen receptors[6]. In a placebo controlled trial low dose mifepristone (RU 486) has been shown to decrease myoma size as well as symptoms[7]. Reduction in size with mifepristone might be due to the direct effect in reducing number of progesterone receptors. Besides, because of ovarian acyclicity seen with mifepristone, hormonal milieu similar to early follicular phase may also inhibit steroid dependent growth of myoma .in the present study, we had tried the low-dose 10 mg mifepristone daily for 3 months to avoid adverse side effect .The aim of the study was to evaluate the effect ofmifepristone on leiomyoma volume, at this low dose in view of avoiding hysterectomies.

MATERIAL AND METHOD

This prospective study was done at Department of Obstetrics and Gynecology, SMS Medical College and attached hospitals, Jaipur over a period of 1 and 1/2year from april 2017 to 2018 after obtaining approval from Ethic Committee of Institute .Nonpregnant women of 20 to 45 years age group, having ‘symptomatic myomas’ (single or multiple diagnosed by pelvic ultrasonography) who wished to conserve their uterus were selected for the study.

Excessive uterine bleeding was evidenced by either profuse bleeding with flooding or clots or repetitive periods lasting for more than 8 days. All women gave their written informed consent prior to inclusion and accepted the follow-up protocol of the study.

Each woman received the mifepristone 10 mg daily for the 3 months.

Exclusion criteria were very large myomas greater than 15 cm in size, history of hormonal treatment in last 2 month, history of breast cancer or other genital malignancy, adenexal mass, pregnancy, suspicion of leiomyosarcom on sonography, severe renal or liver dysfunction or a contraindication to mifepristone itself. Blood samples were collected for hemoglobin, blood counts, baseline liver and renal function tests, bleeding time, clotting time, along with a detailed baseline pelvic ultrasound, to know the exact number, size, volume and location of myomas and endometrial thickness at the start of treatment. Three largest diameters (A, B and C) were measured in two planes in approximately perpendicular axis in all myomas. As most of myomas are spherical or ellipsoidal, therefore volume was calculated using formula $0.523 \times A \times B \times C$. In case of multiple myomas largest one (dominant) was used for volume calculations and follow-up. Sonography and hematological parameters were carried out every follow-up visits. Women were asked to keep daily records of bleeding and symptoms as pain, pressure or any side effect during study. Severity of pain was graded according to VAS score.

After 3 months, drug mifepristone was withdrawn but cases were followed up similarly for next 3 months posttreatment phase. Data were collected, tabulated and analyzed using appropriate statistical methods.

RESULT

In our study total 100 cases were enrolled over 1 and ½ year from april 2017 to 2018 from Department of Obstetrics and Gynecology, SMS Medical College and attached hospitals, Jaipur. majority of patients were in the age group 30–40 years (58%). mean age was 37.59 ± 6.02 years .Majority of cases were from urban area, Hindu religious, class iii socio-economic status, illiterate .Most of patients were parity 2 (44%) . most of patient presented with complain of menorrhagia (84%) symptom, followed by pelvic pressure (56%), dysmenorrhoea (60%), metrorrhagia (35%), pain in lower abdomen (40%), bladder symptoms (28%), backache (20%), dyspareunia (15%) for which they came to hospital .

Menorrhagia improved by 100% caases and all patients(100%) developed amenorrhoea during the treatment this is important effect in patients with menorrhagia. All patients were resumed regular menstrual cycle with in 21.01 ± 4.41 days after stopping treatment.

Table 1: Change in blood loss after treatment with Mifepristone 10 mg assessed by Pictorial blood loss assessment chart (PBAC)

PBAC	Baseline		1 month		3 month		6 month		P value
	N	%	N	%	N	%	N	%	
≤50	8	8	100	100	100	100	87	87	<0.001 (S)
51 – 100	10	10	0	0	0	0	0	0	
101-150	68	68	0	0	0	0	13	13	
151-200	14	14	0	0	0	0	0	0	
Total	100	100	100	100	100	100	100	100	
Mean±SD	121.2 ± 35.9		16.7 ± 11.5		0		33.2 ± 30.2		
P value*	-		<0.001 (S)		<0.001 (S)		<0.001 (S)		

***compared to baseline**

baseline PBAC Mean ± SD of 121.2 ± 35.9 decreased to (16.7 ± 11.5) after one month and was 0 at 3 months follow up. At 6 months the PBAC was (33.2 ± 30.2). This decrease in PBAC was found to be statistically significant at all follow up time ($p<0.001$). Increase in Hb levels after 3 month of treatment which was increased from baseline value of 8.38 ± 0.78 gm/dl to 10.02 ± 0.78 gm/dl (19.57%).

there was significant changes in ET from a baseline value of 5.60 ± 0.97 mm to 6.70 ± 1.63 mm. Histopathology findings before starting treatment endometrial biopsy reveal secretory endometrium (63%), proliferative endometrium (32%) and simple hyperplasia without atypia was (5%) .after 3 month of treatment (55%) cases were proliferative phase followed by simple hyperplasia and secretory endometrium 27% and 18% and there were endometrial hyperplasia but no atypical hyperplasia was observed in any of cases.VAS score was decreased from 5.39 ± 1.55 to 0.33 ± 0.71 at 3 months and was 1.13 ± 0.76 at 6 months follow up in,this decrease in VAS was found to be statistically significant at all follow up time ($p<0.001$). Size of fibroid volume reduced from 62.89 ± 34.69 to 54.57 ± 33.14 (15.14 ± 2.96%) after one month, but this decline was not statistically significant ($p=0.37$). It decreased further to 45.34 ± 28.43 (30.11 ± 5.21%) at 3 months and was 46.21 ± 28.92 (by 28.81 ± 6.00%) at 6 months follow up, after stopping the treatment at 6 month slight increase in fibroid volume but it was less than baseline volume. This decrease in fibroid volume was found to be statistically significant at 3 and 6 months follow up time ($p<0.001$). Percentage reduction in fibroid volume was more in patients treated with Mifepristone 25 mg as compared to 10 mg at both 3 months and 6 months it was significant ($p<0.001$)

Table 2 Change in fibroid volume after treatment with Mifepristone 10 mg

Fibroid volume (cm^3)	Baseline		1 month		3 month		6 month		P value
	N	%	N	%	N	%	N	%	
≤50	48	48	53	53	61	61	60	60	<0.001 (S)
51 – 100	42	42	40	40	35	35	35	35	
101-150	6	6	5	5	2	2	3	3	
151-200	2	2	0	0	2	2	2	2	
>200	2	2	2	2	0	0	0	0	
Total	100	100	100	100	100	100	100	100	
Mean±SD	62.89 ± 34.69		54.57 ± 33.14		45.34 ± 28.43		46.21 ± 28.92		
P value*	-		0.37		<0.001 (S)		<0.001 (S)		

***compared to baseline**

DISCUSSION

Medical treatment reduces size, builds up hemoglobin and even renders surgery unnecessary, if in term the patient is going to enter menopause because fibroid being a hormone-depended tumor stops to grow after menopause.

Excessive abnormal vaginal bleeding is the most common symptom reported with myoma leading to iron deficiency anemia in women. We found that some, very small myomas also lead to significant menorrhagia. Study by Saharan S et al (2016)8 reported that excessive vaginal bleeding was reported by 82% cases, followed by backache & pain abdomen by 72% & 52% cases, respectively. Among AUB, 48% cases presented with menorrhagia while 32% and 4% presented with polymenorrhagia & menometrorrhagia, respectively. Hari A et al (2017)[9]study found that after completing 3 months of treatment, menorrhagia, dysmenorrhea and abdominal pain decreased by 95.3%, 91.5% and 78.2% respectively. About 86% of patients were amenorrhoeic at the end of 3 months of treatment.

study by Saharan S et al (2016)[8], mean PBAC score was reduced for 111.52 at enrollment to 2.36 at the end of 3rd month of therapy . In our study response with 10 mg dose of mifepristone was found to be quiet effective in reducing myoma size to 30.11% of baselin over the period of 3 months.

Similarly in study done by Saharan S et al (2016)[8], the mean (range) baseline fibroid volume was 91.13 (30.77-432.70) cm^3 at the time of recruitment. The mean (range) fibroid volume at the end of the 1st month was 66.48 (17.41 - 371.75) cm^3, while at the end of 3rd month was 38.73 (2.763-146.94) cm^3 ($p<0.006$). The maximum no. of cases was presented with the fibroid volume ≤50 cm^3.Dose of 10 mg was selected to decrease the unnecessary side effect and found satisfactory in relieving menorrhagia, pain abdomen, improving hemoglobin and thus avoiding need for blood transfusion in our study.

Mechanism of reduce bleeding and myoma size is likely to be due to structural functional and microvascular effects of mifepristone on the endometrium and uterine musculature.

System review of past studies had shown endometrial hyperplasia as the notable adverse effect of the drug mifepristone.10 Long-term use of high dose of antiprogesterone may promote an unopposed estrogen milieu leading to endometrial hyperplasia.11 this short-term treatment is well-tolerated, although large long-term studies are needed to add safety information, about endometrial and breast proliferation and follow-up after stopping treatment. In a reproductive age

female medical therapy results may not be as good, as myoma may regrow after discontinuation of treatment. Typically, best candidates are perimenopuasal women with anemia and those who want to avoid surgery. It can be given preoperative cases to reduce size and build up hemoglobin level.

CONCLUSION

Study supports that 10 mg mifepristone daily for 3 months is effective in alleviating hysterectomy and even for presurgical management of myoma-related bleeding by inducing amenorrhea, increasing hemoglobin and reducing myoma volume.

REFERENCES

1. Adamson GD. Treatment of uterine fibroids current findings with gonadotropin releasing hormone agonists. Am J Obstet Gynecol 1992; 166 : 746-51.
2. Carlson KJ, Nichols DH, Schiff I. Indications of hysterectomy. N Engl J Med. 1993; 328 : 856-60.
3. Raghav V, Singh Y, Shankar P, Dixit RK. Role of mifepristone in conservative management of fibroid uterus. World Journal of Pharmaceutical Sciences. ISSN (Print) : 2321-3310; ISSN (Online) : 2321-3086.
4. Lethaby A, Vollenhoven B, Sowter M. Preoperative GnRH analogue therapy before hysterectomy or myomectomy for uterine fibroids. Cochrane Database Syst Rev. 2001: CD000547.
5. Ishikawa H, Ishi K, Serna VA, Kakazu R, Bulun SE, Kurita T. Progesterone is essential for maintenance and growth of uterine leiomyoma. Endocrinology, 2010; 151: 2433-42.
6. Spitz IM. Clinical utility of progesterone receptor modulators and their effect on the endometrium. Curr Opin Obstet Gynecol. 2009; 21: 318-24.
7. Engman M, Granberg S, Williams AR, Meng CX, Lalitkumar PG, Gemzell-Danielsson K. Mifepristone for treatment of uterine leiomyoma. A prospective randomized placebo controlled trial. Hum Reprod. 2009; 24 : 1870-9.
8. Saharan S, Khajotia S, Falodia S, Budania S, Prakash P. A Prospective Study to Evaluate the Effect of Mifepristone on Reduction of Size of Uterine Fibroid. IOSR Journal of Dental and Medical Sciences (IOSR-JDMS). e-ISSN: 2279-0853, p-ISSN: 2279-0861.May 2016; Volume 15, Issue 5 Ver. VIII : PP 69-73.
9. Hari A, Sruhya M. A Prospective and Interventional Study of the Role of Low Dose Mifepristone in the Management of Uterine Leiomyoma in Perimenopausal Women. Saudi Journal of Medical
10. Newfield RS, Spitz IM, Isacson C, New MI. Long-ter mifepristone (RU486) therapy resulting in massive benig endometrial hyperplasia. Clin Endocrinol 2001;54:399-404.
11. Steinauer J, Pritts EA, Jackson R, Jacoby AF. Systematic revie of mifepristone for the treatment of uterine leiomyomata. Obst Gynecol 2004;103:1331-36.