International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Seher U et al. Int J Reprod Contracept Obstet Gynecol. 2018 Dec;7(12):4853-4857
www.ijrcog.org

pISSN 2320-1770 | eISSN 2320-1789

DOI: http://dx.doi.org/10.18203/2320-1770.ijrcog20184928

Original Research Article

Study the effect of mifepristone on clinical symptoms and its side effects in patients with fibroid uterus

Umbreen Seher, Nidhi Chauhan*, Mishu Mangla

Department of Obstetrics and Gynecology, Himalayan Institute of Medical Sciences, SRHU, Dehradun, Uttarakhand, India

Received: 06 November 2018
Accepted: 16 November 2018

***Correspondence:**
Dr. Nidhi Chauhan,
E-mail: manumanan@rediffmail.com

ABSTRACT

Background: Fibroid can lead to a variety of clinical symptoms including pain, menorrhagia, and lump in abdomen. The availability of a safe and efficient medical management options for symptomatic fibroid is of considerable clinical and public health importance. The present study is designed to see the safety and efficacy of mifepristone in the medical management of uterine fibroids.
Methods: The study was conducted in the Department of Obstetrics and Gynaecology, Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun over a period of 12 months. A total of 40 patients were included in the study.
Results: Amount of bleeding was assessed by PBAC score, which significantly reduced by 83.9% at the end of treatment. And 62% patients developed amenorrhoea due to mifepristone. Similarly, pain abdomen/dysmenorrhoea was assessed by Numeric Pain Rating Scale, which also showed a significant reduction in 55% patients with no pain at the end of 3 months.
Conclusions: The study clearly shows that Mifepristone is a safe and effective option to manage fibroid uterus and its associated symptoms.

Keywords: Clinical symptoms, Fibroid, Mifepristone

INTRODUCTION

Fibroid can lead to a variety of clinical symptoms including pain, menorrhagia, and lump in abdomen. Anterior wall fibroids can cause pressure symptoms on the bladder and increased frequency of micturition. Posterior wall fibroids lead to spontaneous abortions, infertility etc. The severity of symptoms mainly depends on number of fibroids, their size and site.[1] The availability of a safe and efficient medical management options for symptomatic fibroid is of considerable clinical and public health importance. New technologies have given additional minimally invasive techniques as cryoablation, percutaneous laser ablation, "magnetic resonance imaging (MRI)-guided focused ultrasound" and transvaginal uterine artery ablation are currently under trial. Recently, new medications have been proposed, and are used as long-term medical therapy options for symptomatic fibroids.[2]

"Mifepristone" (RU 486) on the other hand is described as a "progesterone receptor modulator" with antagonistic action. It inhibits the progesterone receptors by strongly binding to them, and little bit to the "estrogen receptors" and upregulates the "androgen receptors".[3] It is synthesized from its precursor norethindrone, and competitively binds and inhibits the progesterone receptors.4 It also leads to amenorrhoea by delaying or inhibiting ovulation. It reduces the menstrual blood loss by causing direct suppressive action on the endometrium

as well as on reduction of the stromal vascular endothelial growth factor (VEGF).[5] In recent days, fibroid uterus has become a common finding on ultrasound, which requires treatment. The present study is designed to see the safety and efficacy of mifepristone in the medical management of uterine fibroids.

METHODS

The study was conducted in the Department of Obstetrics and Gynaecology, Himalayan Institute of Medical Sciences, Swami Ram Nagar, Dehradun over a period of 12 months. Subjects were recruited from Obstetrics and Gynaecology OPD at Himalayan Institute of Medical Sciences, Dehradun, after taking a written and Informed consent. Follow up of each subject was done for 3 consecutive months.

The type of the study was experimental, pre and post. Sample size of the study includes 40 subjects with uterine leiomyoma from the Obstetrics and Gynaecology OPD over a period of one year and follow up was done for 3 months.

Inclusion criteria

Women of reproductive age group (18-49years) with

- Symptomatic fibroids
- Asymptomatic patients showing fibroid of size >2.5cm on ultrasonography.

Exclusion criteria

- Presence of pregnancy or lactation
- Women desirous of pregnancy
- Suspicious of uterine, ovarian or endometrial malignancies
- H/o hormonal treatment over past 3months
- Presence of any renal, respiratory or heart disease, PID or any other adnexal pathology
- Uterine fibroid >20weeks size
- Atypical endometrial hyperplasia
- Those having contraindication for use of mifepristone.

Study tools: Relevant medical, obstetric and menstrual history was taken, past illness if any, relevant personal history, family history, was also be included.

- Case reporting form
- Endometrial biopsy curette
- Histopathology
- Ultrasonography
- Blood investigations- Haemoglobin, Liver function Test, Kidney function test, TSH
- Pictorial blood loss assessment chart (PBAC)
- Numeric pain rating scale.

RESULTS

The most common complaint associated with fibroid uterus was menorrhagia in 24(60%) cases. 8(20%) cases were asymptomatic, but with a fibroid of >2.5cm. Pain abdomen and dysmenorrhoea were seen in 8(20%) patients (Table 1).

Table 1: Symptom wise distribution of cases.

Symptoms	Frequency (n=40)	Percentage
Menorrhagia	24	60
Pelvic pain/ dysmenorrhoea	8	20
Asymptomatic	8	20
Total	40	100

In this study, mean baseline PBAC score decreased by 71.20% at 1month and significantly by 83.29% at the end of 3 months treatment with Mifepristone. 29 patients had menorrhagia at the time of recruitment, out of which 18 patients (62%) developed amenorrhoea at 1 month, which continued till 3months of treatment with mifepristone in 37(92.5%) the PBAC score was between 0-50 at the end of treatment (Table 2).

Table 2: Comparison of cases according to PBAC score (n=40).

PBAC score	At 0 month		At 1 month		At 3 months	
	No.	%	No.	%	No.	%
0-50	19	47.5	33	82.5	37	92.5
51-100	6	15	5	12.5	2	5
101-150	9	22.5	2	5	1	2.5
151-200	2	5	0	0	0	0
> 200	4	10	0	0	0	0
Mean	79.28±70.90		22.83±37.13		13.00±24.43	

In this study, there was a significant reduction in pain score with treatment. 55% patients had no pain in 22.5% patients the pain score was 2.

Table 3: Comparison of cases according to Pain Score (n=40).

Pain score	At 0 month		At 1 month		At 3 months	
	No.	%	No.	%	No.	%
0	0	0	22	55.0	22	55.0
2	3	7.5	3	7.5	9	22.5
3	1	2.5	3	7.5	6	15.0
4	8	20.0	8	20.0	3	7.5
5	8	20.0	2	5.0	0	0
6	6	15.0	2	5.0	0	0
7	4	10.0	0	0	0	0
8	10	25.0	0	0	0	0
Total	40	100	40	100	40	100

Significantly there were no patients in the pain score level from 5 to 8 at the end of treatment (Table 3). In this

study, total 40 patients were taken, out of which 4 patients were unmarried, therefore, endometrial biopsy was not done in them, and were excluded. Post-treatment, 1 (2.7%) out of 36 cases developed endometrial hyperplasia, which was simple hyperplasia without atypia (Table 4).

Table 4: Endometrial changes before and after treatment.

HPE report	Before treatment		After treatment	
	Frequency (n=36)	Percent	Frequency (n=36)	Percent
Atrophic endometrium	1	2.7	0	0.00
Endometrial Hyperplasia	0	0.00	1	2.7
Late secretory phase	5	13.8	4	11.16
Post ovulatory phase	2	5.5	0	0.00
Proliferative phase	13	36.1	26	72.22
Secretory Phase	15	41.6	5	13.8
Total	36	100.0	36	100.00

Table 5: Side-effects of treatment.

Side effects	At 1 month		At 3 months	
	Frequency (n=40)	Percentage	Frequency (n=40)	Percentage
Nausea	4	10	8	20
Vomiting	1	2.5	2	5
Diarrhoea	2	5	2	5
Hot flushes	1	2.5	2	5
Weight gain	2	5	4	10
Mood swings	3	7.5	6	15
Headache	9	22	13	32
Weakness	14	35	19	47
Fatigue	13	32	18	45
Loss of libido	0	0	0	0

Most common side-effect of mifepristone in present study was weakness and fatigue, which increased with treatment. At 1month weakness was seen in 35% cases, which increased to 47% at 3 months. And Fatigue increased from 32% at 1month to 45% at 3 months. Other side effects as nausea, vomiting, mood swings were also present, but less common. The percentage of cases with diarrhoea were same (5%), before and after 3 months of treatment. No case experienced loss of libido in present study (Table 5).

DISCUSSION

In present study, menorrhagia was the most common fibroid related symptom seen in 60 per cent patients. Pain abdomen and dysmenorrhoea was seen in 20% patients. Seth et al. in their study found that abnormal and excessive uterine bleeding was the commonest problem seen in 77 patients (93.96%) followed by heaviness in lower abdomen in 22 (26.83%) and pain in 18 (21.95%) for which they came to hospital.[6] Another study conducted by Sinha et al. showed that 40 per cent patients had menorrhagia as the major complaint, followed by pain abdomen in 26 per cent.[7] Therefore, it was concluded that menorrhagia is the most common symptom associated with uterine fibroid.

We saw that in present study, there was a significant decrease in the mean PBAC score. There was a decrease by 71.20% at 1 month of treatment, and by 83% at the end of 3 months of treatment. And 62 per cent patients became amenorrhic at the end of treatment.

Kulshrestha et al. in their study showed that the PBAC score significantly declined from 253 to 19 in patients who were given 25 mg mifepristone daily. And the PBAC score declined from 289 to 104 in patients who were given 10mg mifepristone daily, after 3 months of completion of the treatment.[1] Sabita et al. did a study in which the mean blood loss was corrected in 100% of the patients.[8] Another study by Eisenger et al. showed that there was a significant difference of 7. 1units in the menstrual blood loss index in the two groups after treatment.[9] One more study conducted by Arora et al. it was found that all patients became amenorrhic at the end of treatment, resulting in a PBAC score of "zero".[10] This concluded that mifepristone is an effective choice of treatment for fibroid and related symptoms in

perimenopausal age group and in patients who want to avoid surgical treatment.

In present study another important complaint was pelvic pain. The results showed that there was a significant reduction in pain, as measured by the "Numeric Pain Control Scale". By the end of 3 months of treatment, 55 per cent patients were completely relieved of pain. In one study by Fiscella et al. there was no significant improvement in pain, when assessed by the "McGill pain questionnaire".[11] Shikha Seth et al. gave 25mg mifepristone daily for 3 months. The results showed a significant decline in the symptom of pain, which was "4" at baseline to "2" at the end of treatment.[6]

In present study, no patient had endometrial hyperplasia at baseline, but one patient developed endometrial hyperplasia at the of end treatment, though it was without atypia. The volume of the fibroid also increased in this patient, and later ended up with hysterectomy. Bagaria et al. conducted a study, which showed that all patients had normal endometrium (proliferative or secretory) at the time of enrollment. And later after completion of the treatment, 12 of the 19 patients (63.1%) who were given mifepristone developed endometrial hyperplasia compared the placebo group in which no patient had hyperplasia. Out of these 12 patients, one patient developed complex hyperplasia, while the rest developed simple hyperplasia without atypia.[12] Seth et al. conducted a study in which 25mg mifepristone was given daily for a period of 3 months. Only 2 patients had a endometrial thickness of more than 20 mm. They underwent endometrial biopsy, and the histopathology showed simple hyperplasia.[6] In present study, many side effects of the drug were studied. The results concluded that 2 patients (5%) had hot flushes at the end of treatment, and the most common side-effect was weakness present in 19 patients (47%). Kulshrestha et al. did a study in which the most common side-effects were hot flushes (7.1%) and weakness (7.1%).[1]

Sudha et al. in their study showed that the only side effect present was fatigue, seen in 6 patients.[13] In present study, fatigue was present in 18 (45%) patients at the end of treatment with Mifepristone, and was a significant side effect. In a study by Bagaria et al there were no side-effects like nausea, vomiting, fatigue, headache, weakness, hot flashes, diarrhoea, loss of libido in any patient after giving 10mg mifepristone.[12] But in present study, almost all side effects were present. Loss of libido was the only side effect not seen in any of the patient before and after the treatment.

CONCLUSION

A significant reduction was seen in major symptoms i.e menorrhagia and pain after treatment with mifepristone and the side effects were minimal and not significant. The study shows that mifepristone is a safe and effective option to manage fibroid uterus and its associated symptoms, although long term follow up studies are required to study the recurrence of symptoms after stoppage of treatment.

ACKNOWLEDGMENTS

Authors would like to thank Mr. Deepak Kumar for his support during study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Kulshrestha V, Kriplani A, Agarwal N, Sareen N, Garg P, Hari S, et al. Low dose mifepristone in medical management of uterine leiomyoma - an experience from a tertiary care hospital from north India. Indian J Med Res. 2013;137(6):1154–62.
2. Tropeano G, Amoroso S, Scambia G, Levy BS. Management of Uterine Fibroids. Hum Reprod Update. 2007;14(3):812-23.
3. Spitz IM. Mifepristone: where do we come from and where are we going? Clinical development over a quarter of a century. Contracep. 2010; 82(5):442-52.
4. Cadepond, PhD F, Ulmann, MD, PhD A, Baulieu, MD, PhD EE. RU486 (mifepristone): mechanisms of action and clinical uses. Ann Review Med. 1997;48(1):129-56.
5. Narvekar N, Critchley HO, Cheng L, Baird DT. Mifepristone induced amenorrhoea is associated with an increase in microvessel density and glucocorticoid receptor and a decrease in stromal vascular endothelial growth factor. Hum Reprod. 2006;21(9): 2312-8.
6. Seth S, Goel N, Singh E, Mathur AS, Gupta G. Effect of mifepristone (25 mg) in treatment of uterine myoma in perimenopausal woman. J Midlife Health. 2013;4(1):22-6.
7. Sinha M, Kyal A, Mukhopadhay P. Effectiveness of Mifepristone in the Treatment of Uterine Leiomyomata. Nepal J Obstet Gynaecol. 2013 ;8(1):22-5.
8. Das SS. Prospective Study on Low-Dose Mifepristone for the Treatment of Leiomyoma: A Hospital Based Study. Int Arch BioMed Clinic Res. 2018 21;4(1):104-6.
9. Eisinger SH, Fiscella J, Bonfiglio T, Meldrum S, Fiscella K. Open-label study of ultra ow-dose mifepristone for the treatment of uterine leiomyomata. European J Obstet Gynecol Reproduct Biol. 2009;146(2):215-8.
10. Arora D, Chawla J, Kochar SP, Sharma JC. A randomized control trial to assess efficacy of Mifepristone in medical management of uterine fibroid. Med J Armed Forces India. 2017;73(3):267-73.

11. Fiscella K, Eisinger SH, Meldrum S, Feng C, Fisher SG, Guzick DS. Effect of mifepristone for symptomatic leiomyomata on quality of life and uterine size: a randomized controlled trial. Obstet Gynecol. 2006;108(6):1381-7.
12. Bagaria M, Suneja A, Vaid NB, Guleria K, Mishra K. Low-dose mifepristone in treatment of uterine leiomyoma: a randomised double-blind placebo-controlled clinical trial. Aust NZJ Obstet Gynaecol. 2009;49(1):77-83.
13. Sudha B, Kumari D. effect of low dose mifepristone in symptomatic uterine leiomyoma. J Evidence Med Healthcare. 2016;3(21):909-13.

Cite this article as: Seher U, Chauhan N, Mangla M. Study the effect of mifepristone on clinical symptoms and its side effects in patients with fibroid uterus. Int J Reprod Contracept Obstet Gynecol 2018;7:4853-7.