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# EFFECT OF MIFEPRISTONE IN THE TREATMENT OF UTERINE MYOMA IN PERIMENOPAUSAL WOMEN

Gynaecology

**Dr. Vikrant Gupta** Lecturer, Department of Radio Diagnosis, Government Medical College and Hospital, Jammu.

**Dr. Sonika Gupta*** Consultant gynaecologist, Department of Gynaecology, District Hospital, Udhampur, Jammu. *Corresponding Author

**Dr. Shivani Gupta** Medical Officer, Department of Radiology, Government Hospital, Sarwal, Jammu.

## ABSTRACT

**Objectives: -** To evaluate the effect of mifepristone (25mg) on symptomatic myoma in perimenopausal women.

**Material and Methods: -** 50 perimenopausal women of age 35-50years having symptomatic myoma were selected form Gynecology OPD and given 25mg Mifepristone once daily continuously for three months. Variables as baseline uterine size, uterine volume, myoma size, volume, their number, position, characteristics, hemoglobin and blood parameters were taken and followed monthly for six months. Bleeding and pain scores were checked on monthly visits. Changes in above parameters were tabulated during the first three months treatment phase and then next three months post treatment phase for analysis.

Statistical Analysis: - Was done by calculating mean, standard deviation, standard error and percentage distribution of variables.

**Results: -** Menorrhagia was the most common symptom which led patients to report to hospital. Mean uterine volume reduced to 63.69% of base line, Mean dominant Myoma volume reduced to 53.61% of base line and hemoglobin raised to 137% after complete three months of treatment. Changes persisted in next three months post-treatment follow-up, while hysterectomy was required in one case.

**Conclusion: -** Three Months treatment of 25mg Mifepristone effectively controls bleeding, reduces the uterine and myoma volume and thus can avoid blood transfusion and hysterectomy in a lot of symptomatic myoma cases.

## KEYWORDS

Antiprogestogen, Medical treatment, Mifepristone, Myoma.

**INTRODUCTION**: -

Leiomyoma is the common benign tumor of uterus occurring in up to 20% of women with maximum incidence between 35-45years of age leading to menorrhagia, pain and lump in abdomen {1}. Severity of symptoms typically depends on size, number of myomas and their location. It is one of the most frequent indications of operative procedures in women of reproductive age.

Others treatment modes for uterine myoma includes- Myolysis, embolization of feeding arteries (invasive), while current medical management options are GNRH agonist and antagonist, selective estrogen receptors modulators (SERM), Aromatase inhibitors, Danazol, Gestrinone, Antiproge stogens and progesterone receptor modulators (SPRMS) etc. None of the drug has been approved by FDA for the treatment of myoma yet. Long term treatment with GnRH agonist treatment is problematic because of its high cost and significant side effects due to hypoestrogenic environment produced by it.

Mifepristone is a sympathetic steroid with anti-progesterone and anti-glucocorticoid activities. The aim of the study was to evaluate the effects of 25mg Mifepristone on uterine and myoma volume, hemoglobin and symptomatic improvement in view of avoiding hysterectomy and blood transfusions in perimenopausal women. In the present study, we had tried 25mg dose for short period of three months for speedy symptomatic recovery.

**MATERIALS AND METHODS**: -

This study was done at Department of Gynecology, District Hospital, Udhampur, Jammu over a period of 1 year from April 2018 to April 2019. In this study, non-pregnant women of 35-50 years age (peri-menopausal) group, having "symptomatic Myomas "(single or multiple diagnosed by pelvic sonography) who wished to conserve their uterus were enrolled for the study. Excessive uterine bleeding was evidenced by passage of clots, repetitive periods lasting for more than 8 days or cycle length less than 21 days leading to anemia. Hemoglobin less than 11gm% and hematocrit less than 30% was taken as criteria for anemia. (Mild 11-10gm%, Moderate 10-7%, severe less than 7gm% and decompensated if less than 4gm%). All women give their written informed consent prior to inclusion and accepted the follow up protocol of the project. Each woman received the Mifepristone 25mg daily for the three months starting from the 3rd to 5th day of menstrual cycle from the hospital.

Exclusion criteria were very large myomas greater then 10cm in size, history of hormonal treatment in last 2 months, history of breast cancer or other genital malignancy, pelvic inflammatory disease (PID), adnexal Mass, pregnancy, suspicion of leiomyosarcoma on ultrasonography or any contra indication to mifepristone itself as hypersensitivity, severe renal or hepatic disorders.

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 size and volume of uterus, number, size, volume and location of myomas and endometrial thickness at the start of treatment and then four weekly follow up. Three largest diameters (A, B & 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 x A x B x C. In case of multiple myomas largest one (dominant) was used for volume calculations and follow up. Viscosmi formula was used for the uterine volume that is $4/3\pi$ W/2 x L/2 x T/2, where W is uterine width on transverse section at uterine fundus, L is uterine length on sagittal section from internal OS to fundus and T is uterine thickness measured on sagittal section between the anterior and posterior walls. Women were asked to keep daily records of bleeding and symptoms as pain, pressure or any side effects on a table calendar. Symptoms were graded at every visit on a five-point "Likert scale" (0= no symptom, 1= light, 2= moderate, 3= severe and 4= very severe). After three months drug Mifepristone was withdrawn but cases were followed up similarly for next three months in post treatment phase. Data were collected, tabulated and analyzed using appropriate statistical methods.

**RESULTS**: -

Total 50 cases were enrolled over 1 year from April 2018 to April 2019 from Gynecology OPD of District Hospital Udhampur, Jammu. Mean age was 38.45 ± 2.5years.

Demographic parameters are shown in table 1.

**Table 1: -**

| PARAMETERS | NO = 50 |
|---|---|
| Mean age | 38.45 year ± 2.5 |
| Median parity | 3 (2-5) |
| Mean BMI | 23.11kg/m2±3.80 |
| CASTE | |
| Hindu | 40 |

| | |
|---|---|
| Muslim | 8 |
| Christian | 1 |
| Sikh | 1 |
| **Socio-Economic state** | |
| Class I | 2 |
| Class II | 3 |
| Class III | 18 |
| Class IV | 27 |
| Education | |
| Illiterate | 22 |
| Primary | 5 |
| Tenth standard | 15 |
| Graduate | 8 |
| **Myoma** | |
| Sub serous | 2 |
| Intra mural | 42 |
| Submucosal | 6 |

Abnormal and excessive uterine bleeding (AUB) was the commonest problem reported by 47 cases (94%) followed by heaviness in lower abdomen in 12 (24%) and pain in 10 (20%) for which they came to hospital. Among AUB, 54% was menorrhagia, 26% poly menorrhagia and 12% reported menometrorrhagia. Amount of bleeding was not exactly found co-related with size of myoma in our study. 22 (44%) women myomas presented with normal cycles and one (2%) with hypomenorrhea. Bleeding stopped within 4-5days of start of mifepristone and 45 women (90%) had complete amenorrhea during treatment phase. 1 women (2%) did not respond to drug and their myoma volume continued to increase progressively and had hysterectomy done later. Dysmenorrhea, pelvic pain, heaviness, backache and urinary complaints improved a lot in first month of treatment. Symptoms scores for pain showed significant change from average (four) at start of treatment to (two) at end of treatment. No significant changes were observed in liver enzymes or renal profile of case.

Leiomyomas with size less than 5mm mostly disappeared and above that has their mean volume reduced by 53.4% of baseline(SD±) after three months of complete treatment. Hemoglobin count improved significantly to 11.07gram % from mean 8.3 gram% at start. Endometrial thickness(ET) increases in all cases during the treatment phase with mean 61.9% over treatment.

Only in one case ET crossed the 20mm mark, after which endometrial biopsy was done and simple endometrial hyperplasia was diagnosed in that case.

Side effects like headache (11%) was noted in first month and hot flush (3.25%) in 2nd month.

**Table 2: -**

| Parameters | Volume ± SD | Mean% ± SE change |
|---|---|---|
| Mean baseline uterine volume | 150135.3 ± 9745.3 | 100% |
| Mean volume at 3rd month | 95621.3 ± 2163.45 | 63.69% ± 22.21 |
| Mean baseline myoma volume | 80357.8 ± 6669.9 | 100% |
| Mean volume at 3rd month | 43911.0 ± 3234.9 | 53.4% ± 48% |
| Mean baseline haemoglobin | 8.3 ± 2.1 gram% | 100% |
| Mean haemoglobin at 3rd month | 11.07 ± 2.8gram% | 137% |
| Mean 3rd month endometrial thickness | 12.35 ± 4.38 | 161.9% |
| Mean baseline endometrial thickness | 7.63 ± 2.71 | 100% |

Menstruation was regained in mean duration of 34.75 (SD ± 18.45) days. One case persisted with amenorrhea and only one required hysterectomy for recurrence of heavy bleeding episodes.

**Table 3: -**

| Post treatment follow up | No. Of cases: - 50 | Percentage |
|---|---|---|
| **Menstruation regained** | | |
| Within one month | 23 | 46% |
| After one month | 26 | 52% |
| **Bleeding** | | |
| Amenorrhoea persisted | 1 | 2% |
| Normal cycle regained | 30 | 60% |
| Heavy required tranexamic acid | 19 | 38% |
| **Operative Treatment** | | |
| Polypectomy | 2 | 4% |
| Recurrent Bleeding required hysterectomy | 1 | 2% |

**DISCUSSION**: -

Fibroid is being a tumor dependent on estrogen and progesterone for its growth. So, the drugs that lower estrogen level like Gnrh agonist, antagonist, Danazol, Gestrinone, Cabergoline, Letrozole, SERM, Anti progesterone (Mifepristone) and selective progesterone receptor modulator (SPRM-Asoprisnil) can be effective in reducing size and symptoms of myoma. Hormonal treatment reduces size, improves hemoglobin (2) by controlling bleedings and renders surgery unnecessary as patient reaches menopause, because fibroid being a hormone dependent tumor stops to grow after menopause. Mifepristone has both antiprogesterone and anti-glucocorticoid properties in dose dependent manner.

Eisinger et al (3) reported fall of 48% in mean uterine volume while amenorrhea in 61% after 6 months of 10mg mifepristone. Another study by kettle et al reported amenorrhea in 40-70% over one year at 5-10mg dose while 100mg leads to 100% amenorrhea (4) AUB ( Abnormal uterine bleeding) is the main reason that worries women as it affects their daily routines, work efficiency and health status, therefore mostly opt for hysterectomy as one-time management in developing countries. With higher doses speedy and better control of bleeding is achieved, this improves the general conditions of women & hemoglobin level, relieves anxiety and provides women a sense of wellbeing and affectivity of treatment but produce hot flushes and other anti-glucocorticoid side effects. Murphy et al (5) had a comparative study of 5mg, 25mg & 50mg dosage and suggested 25mg to be the most effective dose to clinically significant decrease in leiomyoma volume. We choose 25mg daily to achieve rapid symptomatic improvement (improved compliance) in short period of time (3 months) with minimal side effects.

Mechanism of reduced bleeding and myoma size is likely to be due to structural, functional and microvascular effects of mifepristone on the endometrium and uterine musculature in dose and duration dependent manner. In our study 25mg mifepristone reduced uterine size to 63.69% of baseline (- 36.41% decline) while Bagaria et al (6) had 26.6% reduction with 10mg over 3 months and Eisinger et al, 11% with ultra-low dose 2.5mg over 6 months. (7)

Mean myoma volume reduced by 46% with 25mg dose in our study which is quite better than other studies as Engman et al (8). 28% decline with 50mg and kettle et al, (4) 49% decline with 100mg in three months. More number of receptors is there in leiomyoma compared to rest of normal myometrium therefore more steady fall is seen in it.

Endometrial hyperplasia is the notable adverse effect of the drug mifepristone. (9) Long term use of high dose of antiprogesterone may promote as unopposed estrogen milieu leading to endometrial hyperplasia. (10) Keeping the duration short can avoid atypical endometrial hyperplasia and chances of malignant changes. The entry women baseline ET was less than 10mm and after three months has only in one case it became double of it, without any atypia in present study. Hot flush, headache, nausea, fatigue, malaise and rise in liver enzymes, AST & ALT are reported in past studies. (11) This short-term treatment was well tolerated, but large study is needed to add safety information about endometrial and breast proliferation and long term follow up after stopping treatment. In young reproductive age female, medical therapy may not be as good as myoma may re-grow after discontinuation of treatment. Typically, best candidates are peri-menopausal women with anemia and those who want to avoid surgery. It can be used preoperatively to reduce size and build up hemoglobin level to have better surgical outcome. Acceptance rate is high because it is really cost effective. Having a hysterectomy not only causes a surgical trauma but poses a great mental stress to the women.

**CONCLUSION**: -

Most important and useful effect of mifepristone found to be the control of bleeding leading to improvement in hemoglobin level and general conditions. Study supports that 25mg mifepristone daily for three months is effective in alleviating hysterectomy in 87.8% of the women.(12)

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**Conflict of interest**: - NONE DECLARED.

## REFERENCES

1. Salhan Sudha. 1st ed. New Delhi: Jaypee; 2011. Text book of gynecology; pp. 320–1.
2. Sabry M, Hendy AA. Innovative oral treatments of uterine leiomyoma. Obstet Gynecol Int. 2012; 2012:943635.
3. Eisinger SH, Bonfiglio T, Fiscella K, Meldrum S, Guzick DS. Twelve-month safety and efficacy of low dose mifepristone for uterine myomas. J Minim Invasive Gynecol. 2005; 12:227–33.
4. Kettel LM, Murphy AA, Morales AJ, Yen SS. Clinical efficacy of the antiprogesterone RU486 in the treatment of endometriosis and uterine fibroids. Hum Reprod. 1994; 9:116–20.
5. Murphy AA, Morales AJ, Kettel LM, Yen SS. Regression of uterine leiomyomata to the antiprogesterone RU486-dose-response effect. Fertil Steril. 1995; 64:187–90.
6. Bagaria M, Suneja A, Vaid NB, Gulaeria K, Mishra K. Low dose mifepristone in treatment of uterine myoma: A randomized double-blind placebo controlled clinical trial. Aust N Z J Obstet Gynaecol. 2009; 49:77–83.
7. Eisinger SH, Fiscella J, Bonfiglio T, Meldrum S, Fiscella K. Open-label study of ultra-low dose mifepristone for the treatment of uterine leiomyomata. Eur J Obstet Gynecol Reprod Biol. 2009; 146:215–8.
8. Engman M, Granberg S, Williams AR, Meng CX, Lalitkumar PG, Gemzell DK. Mifepristone for treatment of uterine leiomyoma-A prospective randomized placebo controlled trial. Hum Reprod. 2009; 24:1870–9.
9. Newfield RS, Spitz IM, Isacson C, New MI. Long-term mifepristone (RU486) therapy resulting in massive benign endometrial hyperplasia. Clin Endocrinol (Oxf) 2001; 54:399–404.
10. Steinauer J, Pritts EA, Jackson R, Jacoby AF. Systematic review of mifepristone for the treatment of uterine leiomyomata. Obstet Gynecol. 2004; 103:1331–6.
11. Carbonell Esteve JL, Riveron AM, Cano M, Ortiz AI, Valle A, Texido CS. Mifepristone 2.5mg versus 5 mg daily in treatment of leiomyoma before surgery. Int J Women's Health. 2012; 4:75–84.
12. 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; 108:1381–7.