ROLE OF MIFEPRISTONE IN MEDICAL MANAGEMENT OF UTERINE FIBROID

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ABSTRACT: BACKGROUND: Uterine leiomyoma is the most common benign tumour of uterus affecting women of reproductive age group and accounting for most common indication of hysterectomy in India. Effective medical treatment option can prevent hysterectomy related morbidity.

MATERIALS AND METHODS: A total of 50 women with symptomatic leiomyoma and asymptomatic with uterine volume >160cc and fibroid size >2.5cm were included in the study. 20mg/day mifepristone was given to them over period of 3 months. Follow up was done at 1, 3 and 6 months of starting treatment. At each visit patients were evaluated for symptomatic improvement of menorrhagia, dysmenorrhoea and ultrasound for myoma volume, haemogram was done. Endometrial biopsy was done at the beginning of therapy, 3rd month and at end of treatment.

RESULTS: At the beginning of study, all patients had menorrhagia. At 3 months, 80% developed amenorrhea and 20% scanty menses. At 6 months, 56% had scanty menses and 38% had normal menses but none had menorrhagia. 50% of patients had dysmenorrhoea at the beginning of study with severe dysmenorrhoea in 36% of cases. Only 10% of patients at 3 months and 14% at 6 months had dysmenorrhoea. Improvement in haemoglobin percentage from 9.6 gram% to 10.8 gram% at 3 months of therapy. The reduction in mean uterine volume was 12.28%after 1 month, 26.95% after 3 months and 11.13% at end of 6 months, as compared to pre-treatment level. Fibroid volume decreased by 14.34% after 1 month ,29.8% after 3 months and 24.98% at end of 6 months, as compared to pre-treatment level. At the end of 3 months, 50% of patients experienced no side effect. Rest 50% experienced minor side effects like nausea (8%), hot flushes (4%), liver dysfunction as evidenced by mild increase in transaminase (8%) and simple endometrial hyperplasia in 30%. Follow up of these patients at 6 month i.e., 3 months after stopping the drug does not show any evidence of persistence of these effects.

CONCLUSION: 20mg mifepristone produces reduction in myoma size, uterine volume and improvement of symptoms like menorrhagia and dysmenorrhoea. It is administered orally, cost effective and is well tolerable with less side effects.

KEYWORDS: Amenorrhoea, fibroid, leiomyoma, mifepristone, uterine.

HOW TO CITE THIS ARTICLE: Shradha, Archana Kumari, P. B. Sahay. "Role of Mifepristone in Medical Management of Uterine Fibroid". Journal of Evolution of Medical and Dental Sciences 2015; Vol. 4, Issue 88, November 02; Page: 15325-15329, DOI: 10.14260/jemds/2015/2179.

INTRODUCTION: Uterine leiomyoma is the most common benign tumour of uterus affecting 20% of all women of reproductive age group.[1] and leading to 1/3rd of all gynaecological admissions in hospitals.[2] 40% of these patients symptoms severe enough to warrant therapy.[3] Leiomyoma uteri is the most common indication for hysterectomy and accounts for 40% of all hysterectomies in premenopausal women.[4] Although hysterectomy is the only definitive cure for leiomyoma, it has its own morbidity and long term complications. Thus, medical management and minimal invasive techniques are gaining popularity now a days.

These are highly beneficial for young unmarried women who want to avoid surgery, in women having co-morbid conditions contraindicating surgery and in perimenopausal women in whom fibroid volume will regress after menopause. Amongst medical therapy, GnRH agonist which is given as a monthly injection has shown to decrease size of fibroid by 35% and total uterine volume by 30% after 6 months of therapy.[5] GnRH antagonist has rapid action and accounts for 29% decrease in fibroid volume by 3 weeks.[6]

However, these are not widely acceptable as these are costly, administered parent rally and associated with severe hypo estrogenic symptoms and bone loss after prolonged use.7 Moreover, cessation of treatment leads to regrowth of myoma within 4 to 6 months. 7 Danazol decreases uterine volume by 18 to 23% but is associated with androgenic side effect and liver dysfunction.8 LNG-IUS is effective in decreasing fibroid related menorrhagia in 85% cases over 3 months.9

But these can be used only when uterine size is <12 weeks and uterine cavity is normal. Several studies has shown that there is no change in uterine volume with LNG-IUS and expulsion rate is higher amongst patient with fibroid.[10] Uterine artery embolisation decreases size of fibroid, causes symptomatic relief but there is risk of premature ovarian failure and uterine synechiae.[11]

MRgFUS is a new FDA approved non-invasive technique for treatment of uterine myoma. It causes significant improvement of symptoms, decreases fibroid volume by 15% over 6 months and does not compromise future fertility carrier of patient.[12] But it is out of reach of most patients due to high cost of treatment and availability at few tertiary centres only.

Financial or Other, Competing Interest: None.
Submission 29-09-2015, Peer Review 30-09-2015,
Acceptance 20-10-2015, Published 31-10-2015.
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DOI: 10.14260/jemds/2015/2179.

Both estrogen and progesterone plays a vital role in growth of uterine fibroid. In fibroid tissue, as compared to normal myometrium has higher concentration of aromatase enzyme leading to increased local production of estradiol.[13]

Also there is increased expression of progesterone receptor A and B in fibroid tissue and highest mitotic count are found in fibroid tissue at peak of progesterone production.[14] Thus, antiprogesterone like mifepristone, uripristal, asoprisnil and CDB-2914 came under study.[15]

Mifepristone is a progesterone receptor modulator with primarily antagonistic properties. It binds strongly to endometrial progesterone receptors, minimally to estrogen receptors and upregulates androgen receptors.[16] Prospective randomised control trial has shown mifepristone to decrease uterine volume by 48% after 6 months of therapy.[17]

The aim of my study was to highlight the role of mifepristone as a cost effective and safe medical therapy for uterine leiomyoma and also as an alternative to surgery.

MATERIAL AND METHODS: This prospective randomized control trial was conducted on 50 patients attending Outpatient Department of Obstetrics & Gynaecology Rajendra Institute of Medical Science, Ranchi over period of May 2013 to May 2014. Ethical approval from RIMS ethical committee was taken. Informed consent were taken from patients involved in the study group after screening them according to inclusion and exclusion criteria.

Inclusion criteria of my study are women of reproductive age group, symptomatic fibroid, asymptomatic patients with USG showing uterine volume ≥160cc or fibroid size ≥2.5cm and those women who agreed to use non-hormonal method of contraception throughout the study period to prevent pregnancy. Exclusion criteria includes fibroid >12 weeks size, atypical endometrial hyperplasia, associated pelvic pathology, pregnant women and lactating mother and those desirous of pregnancy, those who have used hormonal medication for fibroid or hormonal contraception within last 3 months or having any contraindication to use of mifepristone.

The subjects were given 20mg mifepristone preparation once daily for 3 months. It comes in 200mg tablets, so it was crushed and divided into 10 equal doses for daily administration. They were followed at 1 month, 3 month while on therapy and then at 6 months i.e. 3 months after stopping therapy. At each visit, clinical symptoms, uterine volume, fibroid volume, change in hemoglobin level and side effects were assessed. Endometrial biopsy was done at beginning of study, at 3rd and 6th month.

Evaluation Criteria:

None	Amenorrhea
Scanty	Less than normal bleeding occurs during menstruation
Average	Normal amount of blood loss occurs during menstrual cycle
Heavy	Patient has menorrhagia

Table 1: Symptomatic assessment of menstrual blood loss

None	No dysmenorrhoea
Mild	Analgesic are not required
Moderate	Analgesic may be required, but patient can carry out normal activities
Severe	Patient cannot carry out normal activities, always require pain killers

Table 2: Symptomatic assessment of dysmenorrhoea

3. Hemoglobin percentage, LFT, RFT.
4. Ultrasound with color Doppler for:
   a) Uterine volume – Calculated by Viscosmi formula: $4/3\ \pi\ W/2 \times L/2 \times T/2$
      Where W = Width; L = Length; T = Thickness
   b) Fibroid volume – $4/3\ \pi\ abc$
      Where a, b & c = Radii of sphere.
5. Endometrial biopsy for hyperplasia

RESULTS: At the beginning of study, all patients had menorrhagia. After 1 month of therapy, none of patients had menorrhagia, 18 out of 50 had average menses, 22 had scanty menses and 10 became amenorrhic. At 3 months, 40 out of 50(80%) developed amenorrhea and 10 out of 50 (20%) had scanty menses. At 6 months, 27 out of 50(56%) had scanty menses and 19 out of 50(38%) had normal menses but none had menorrhagia.

DISCUSSION: Mifepristone is a PROGESTERONE RECEPTOR MODULATOR with antiprogestogenic, antiglucocorticoid and weak antiandrogenic activity. It was first synthesized in 1980 by a french company Roussel Uclaf. This was the 38486th compound synthesized by this company hence called RU 38486 or simply RU486. Its use as a treatment option of myoma was first described by Murphy et al in 1993.[18] It was approved for use in India in 2002 by ICMR. Dose of mifepristone ranges from 2.5-50 mg once daily over period of 3-6 month. Lower dose is associated with good symptomatic improvement, minimal side effect but less reduction in myoma and uterine size as compared to higher dose. Other uses of drug are medical termination of pregnancy, emergency contraception, induction of labor, ectopic pregnancy, cushing syndrome, major depression with psychotic illness, glaucoma, meningioma, breast, ovarian and prostate cancer.

Mifepristone is also under trial as an antiretroviral therapy and for chronic multisystem disorder. It is contraindicated in conditions like active liver disease, renal disease, adrenal insufficiency, hemorrhagic disorders, inherited porphyria and in patients on anticoagulant or long-term corticosteroid therapy.

In the present study, 20mg daily dose of mifepristone was found to be effective in relieving symptoms like menorrhagia, dysmenorrhoea; improving anaemia and decreasing mean uterine volume and size of fibroid. Also it is well tolerated without having any serious side effects. Improvement in symptoms was noted as early as in the first month of therapy as also noted in other studies. 2 patient conceived after stopping treatment, indicating that fertility resumes soon after stopping the therapy.

In conclusion, it is good alternative medical therapy in preoperative period as it improves anaemia, reduce size of tumour making surgery technically easier.

It is proved to be a reasonable choice in perimenopausal women in whom myoma regresses after menopause and in the nulliparous women who want to avoid surgery. It can also be used as a preoperative adjunct, especially in patients with severe anaemia and in large fibroid where surgery is technically difficult.

It is not used as a primary medical therapy because of recurrence of symptoms after stopping treatment. However, it has simplicity of oral administration, cost effectiveness and minimal side effects.

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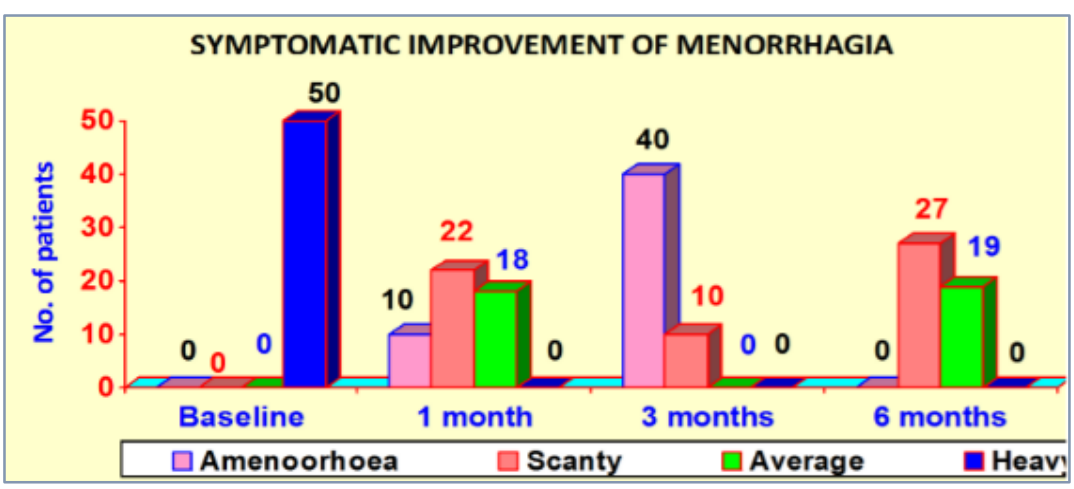
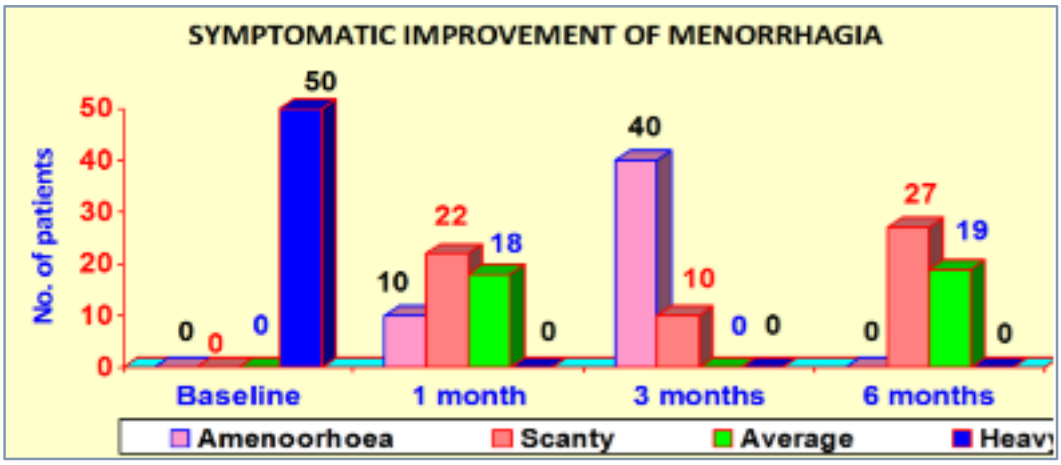
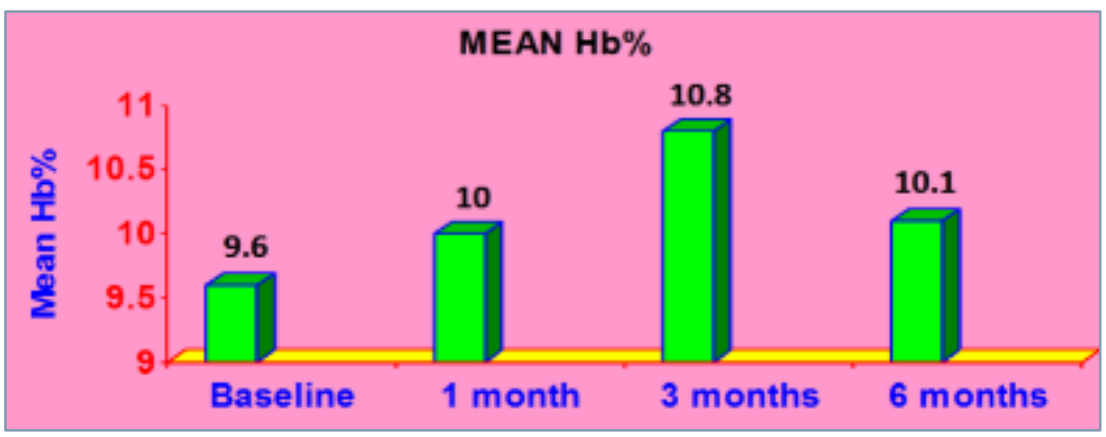


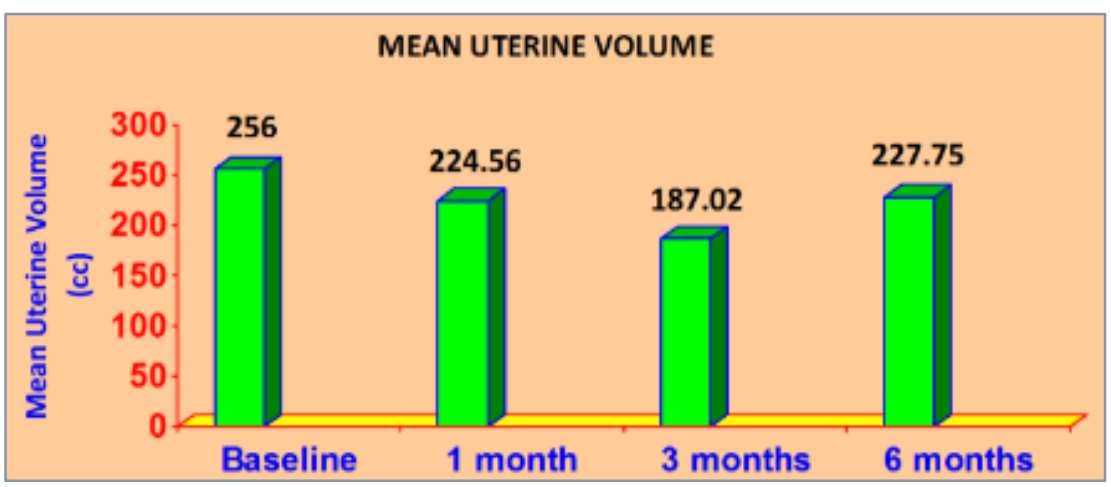
25 out of 50(50%) patients had dysmenorrhoea at the beginning of study with severe dysmenorrhoea in 18(36%) cases. Only 5 out of 50(10%) of patients at 3 months and 7 out of 50(14%) at 6 months had dysmenorrhoea. None had severe dysmenorrhoea even up to 6 months of starting treatment.



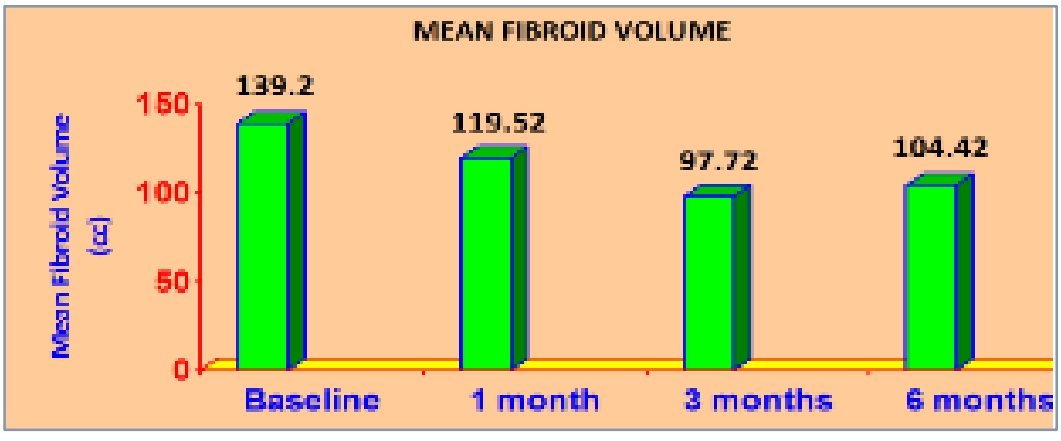
Due to improvement of menorrhagia there was significant increase in mean haemoglobin percentage from 9.6 gram% to 10gm% at 1st month and 10.8 gram% at 3rd months of therapy. Mean haemoglobin level was 10.1gm% at 6th month of therapy i.e., 3 months after discontinuation of drug.



Mean uterine volume was 256 cc at the beginning of therapy. The reduction in mean uterine volume was 12.28%(224.56cc) after 1 month, 26.95%(187.02cc) after 3 months and (227.75cc)11.13% at end of 6 months, as compared to pre-treatment level.



Mean fibroid volume at the beginning of therapy was 139.2cc. Fibroid volume decreased by 14.34%(119.52cc) after 1 month, 29.8%(97.72cc) after 3 months and 24.98%(104.42cc) at end of 6 months, as compared to the pre-treatment level.



At the end of 3 months, 50% of patients experienced no side effect. Rest 50% experienced minor side effects like nausea (8%), hot flushes (4%), liver dysfunction as evidenced by mild increase in transaminase (8%) and simple endometrial hyperplasia in 30%. Follow up of these patients at 6 month i.e., 3 months after stopping the drug does not show any evidence of persistence of these effects.