ORIGINAL RESEARCH PAPER
Volume-8 | Issue-10 | October - 2019 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

MIFEPRISTONE IN THE MANAGEMENT OF UTERINE MYOMA

Gynaecology

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ABSTRACT

Hysterectomy for fibroids is one of the commonest gynaecological surgeries in India. To reduce the morbidity and mortality associated with the surgery a number of medical treatments have been tried. Mifepristone is one of them and is being used in the recent decade as a more or less effective option in the treatment of myoma. This study was undertaken to evaluate the efficacy and safety of low dose mifepristone in medical management of uterine myomas. Women with symptomatic myomas or myoma of more than 5cm were included in this study. They were given oral mifepristone 25mg per day for 3 months. Patients were followed at 1, 3 and 6 months. The prospective clinical trial was conducted from august 2006 to august 2018 at my clinic. It was found that blood loss reduced significantly in 3 months therapy and the effect started from the first cycle onwards. Amenorrhoea developed in 90% - 95% patients which reverted later.

KEYWORDS

Mifepristone, Uterine myoma, Fibroid

INTRODUCTION

Mifepristone (RU486) is a progesterone receptor modulator with primarily antagonistic properties. It binds strongly to endometrial progesterone receptor, minimally to oestrogen receptor and upregulates androgen receptor. In a placebo-controlled trail low dose mifepristone has been shown to decrease myoma size as well as symptoms. Reduction in size with mifepristone might be due to direct effect in reducing number of progesterone receptor. Besides because of ovarian acyclicity seen with mifepristone hormonal milieu similar to earlier follicular phase may also inhibit steroid dependent growth of myoma. Increase in androgen receptors also contributes to antiproliferative effects. Mifepristone also delays or inhibits ovulation which may produce amenorrhoea. Direct suppressive effects on endometrial vasculature endothelial growth factor (VGEF) has also been suggested for reducing menstrual blood loss.

MATERIALS AND METHODS

Women with symptomatic fibroids or myoma >5 cm were selected. Uterine size >20 weeks and fibroids >15 cm were excluded. Routine tests like complete blood count, liver and renal function tests and ultrasound with colour doppler, were performed. A baseline endometrial histology by pipette aspiration was also done. Patients were randomized and were given oral mifepristone 25 mg /day for 3 months. Patients were followed at 1,3 and 6 months.

This prospective randomized clinical trial was performed from August 2016 to August 2018 at my clinic in Patna. Women between 20-50 years of age with single or multiple fibroids were included in the study if they were symptomatic (menorrhagia, dysmenorrhoea, abdominal lump, dull aching abdominal pain, dyspareunia). Other pathology was ruled out with the help of ultrasound. Exclusion criteria remained fibroids of > 20 weeks or > 15 cm size, submucosal fibroids, renal or hepatic dysfunction, suspected adenomyosis, current genital infections, endometrial hyperplasia with atypia and hormonal medications within 3 months and women desiring pregnancy. Complete general and gynaecological examinations was done. Serum oestradiol level was also measured. Number, site, volume of myomas and endometrial thickness was ascertained by ultrasound. Doppler ultrasound helped inn terms of uterine artery resistive index (RI) and pulsality index (PI). Hysteroscopy was performed when endometrial polyp or submucous myomas were suspected. Endometrial aspiration ruled out any abnormal histopathology. Patients were followed up at 1 and 3 months while on therapy and then at 6 months i.e. 3 months after stopping therapy to look at for recurrence of symptoms or regrowth or enlargement of fibroids. On each visit clinical symptoms including bleeding and any side effects were assessed. Amenorrhoea was defined as the absence of menses for two consecutive cycles, USG was done to note the number and size of myomas and endometrial thickness.

At 3 months follow up, haemoglobin, liver function test were repeated. USG colour doppler was done to determine volume reduction and change in blood flow.

RESULTS

A total of 50 patients were recruited and followed up at the gynae outpatient departments after taking informed consent. The 10 patients were lost in follow up before start of treatment, all the women had spontaneous menstrual cycles.

Blood loss reduced significantly from baseline to 3 months therapy and the effect started at the first ever cycle. There was marked relief with significant decrease in bleeding($p<0.01$). 85% developed amenorrhoea , which reverted after a median of 35(5-85) days of stopping therapy. 3 women presented with continuous and heavy bleeding for more than 1 month of effect of mifepristone.

55% presented with abdominal pain before treatment. There was relief of abdominal pain even after 3 months of stopping treatment. There was significant decrease in pain in 33% of patients who presented with dysmenorrhoea at the start of treatment. Twelve patients presented with dyspareunia and this was significantly reduced($p<0.01$). Backache and pelvic pressure improved with treatment. Rectal pain was complained by one patient at the start of therapy, also disappeared with treatment.

Volume of fibroids decreased with treatment. The percentage decrease in overall myoma volume was 32.5% but lesser reduction was observed in multiple myoma (27.5%). At 3 months post treatment follow up, uterine volume further reduced, then uterine size increased again but still lesser than baseline.

At completion of 3 months of therapy, 41% patients had endometrial thickness > 8mm which decreased again at 3 months after stopping therapy. There was significant rise in haemoglobin levels in both the groups with treatment($p<0.05$). Doppler indices RI and PI both increased with treatment, indirectly suggesting decrease in blood flow.

The common side effects were leg cramps, hot flushes, weakness and palpitation

DISCUSSION

Mifepristone is advocated for the treatment of myoma because of its antiproliferative endometrial effect due to its progesterone receptor modulator (SPRM) property. It causes anovulation and amenorrhoea, hence relieving the symptoms of bleeding and pain.

In the present study, 25 mg mifepristone was found to be effective in relieving menorrhagia, pain and others myoma related symptoms. There was size reduction in 3 months duration, though more reduction have been reported in studies of longer duration. Similar results have been reported earlier. Improvement in symptoms was noted as early as

Submitted : 05th June, 2018 | Revised : 23rd June, 2019 | Accepted : 18th August, 2019 | Publication : 01st October, 2019

in the first month of therapy as also reported in other studies. After stopping treatment, symptomatic relief persisting till 3 months. At three months post treatment follow up , uterine volume further reduced. Similar residual improvement has been reported in earlier studies, where author have also reported notable clinical improvement persisting in most patients one year after stopping treatment even though fibroids reached their pre-treatment size. This residual s effect may be due to sometime taken for normalization of the progesterone receptor. Two patients conceived after stopping treatment, indicating that fertility resumes soon after stopping mifepristone.

In the present study, the increase in endometrial thickness seen, might be due to unopposed oestrogenic effect on the endometrium by mifepristone. Once the treatment was stopped, the endometrial thickness normalizes soon. No further volume reduction was seen after six months. Increased rates of breakthrough bleeding or spotting was seen in patients with endometrial hyperplasia.

Intermittent administration has been suggested for long term mifepristone i.e., with treatment duration of 3-4 months followed by an off-drug interval till menstruation occurred. Though it is now known that endometrial thickening with more than three months treatment is due to cystic dilatation and not due to hyperplasia, yet intermittent therapy would be more reassuring to the treating clinician.

The strength of our study were adequate sample size for statistically valid results and inclusions of doppler parameters. Limitation of the study were not using PAEC to clarify endometrial histopathology.

CONCLUSIONS

Our study showed that mifepristone 25 mg, led to symptomatic relief in patients with myoma with more than 90% reduction in menstrual blood loss. 25 mg dose had significantly reduction in overall myoma size as well as in multiple myomas. Endometrial changes specific to progesterone receptor modulator occurred but there was no evidence of atypia. Amenorrhoea developed in 90-95% patients and was reversible. Mifepristone can be reasonable choice especially in perimenopausal women in whom myomas would regress after menopause. Also, in unmarried women who want to avoid surgery, it is the treatment of choice. Although its use as a primary medical therapy is limited due to recurrence after stopping treatment, it can be used as a preoperative adjuvant, especially in patients with preoperative severe anaemia, large fibroids, where surgery is technically difficult or where leiomyoma are unresectable. In addition, some women undergoing hysterectomy, will benefit from a less invasive vaginal rather than an abdominal procedure.

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