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Efficacy of Mifepristone versus GNRH Analogue in the Treatment of Uterine Leiomyoma- A Comparative Study

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Abstract

Background: Uterine fibroids also called as uterine leiomyoma is the most common benign tumor of the uterus. Most women develop one or more uterine leiomyoma during their reproductive years. Hence; we assessed the efficacy of Mifepristone 25mg versus Inj.Leuprolide acetate 3.75mg in reducing size of uterine myoma. **Subjects and Methods:** The study was planned for detecting difference of 15 percent in the outcome variables between the two groups and Standard deviation of 156.00, with 90% statistical power and 5% level of significance, the sample size was calculated to be 70 for the study. The study subjects were randomly assigned into 2 groups of 35 patients each. Group 1: Patients treated with Tablet Mifepristone 25mg once daily for 3 months; Group 2: Patients treated with Inj. Leuprolide acetate depot preparation 3.75mg IM once a month for 3 months. Demographic data, history, clinical examination, details of drug prescription, laboratory investigations and imaging reports were recorded in the study proforma. Various clinical assessment parameters were assessed. **Results:** After three months of treatment, there was a marked relief with significant decrease in visual analog scale score in both the groups ($p < 0.001$). 21 patients (60%) in group 1 and 25 patients (71%) in group 2 presented with mild anemia at the beginning of the study. After three months of treatment, there was a significant ($p < 0.001$) rise in the hemoglobin and hematocrit values in both the groups. There was an increase in mean hemoglobin level by 2.9gm/dl in mifepristone group and 3gm/dl in leuprolide group. **Conclusion:** Treatment with either mifepristone or leuprolide acetate in uterine leiomyoma is safe and causes significant but temporary reductions in uterine size and myoma related symptoms.

Keywords: Leuprolide acetate, Mifepristone, Uterine myoma.

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Introduction

Uterine fibroids also called as uterine leiomyoma is the most common benign tumor of the uterus. Most women develop one or more uterine leiomyoma during their reproductive years. Leiomyoma account for about 40% to 60% of all the hysterectomies performed.[1,2] Myomectomy can be carried out via hysteroscopy, laparoscopy or classically as an abdominal procedure. At present, medical treatments are only used for short-term therapy because of the significant risks with long-term therapy. It is suitable in women with symptomatic leiomyoma in the perimenopausal years or in patients not suitable for surgery due to medical reasons. Drugs are also used as a pre-operative adjunct to reduce the size of leiomyoma, to control bleeding and to improve hemoglobin levels. The reduction in myoma size may also convert a difficult procedure (abdominal hysterectomy) to an easier one (vaginal hysterectomy).[3-5]

Hence; we planned the present study to the efficacy of Mifepristone 25mg versus Inj. Leuprolide acetate 3.75mg in reducing size of uterine myoma.

Subjects and Methods

The present study was conducted to assess patients suffering from symptomatic uterine leiomyoma who attended the Gynecology outpatient department of Sree Narayana Institute of Medical Sciences, Chalakka, Ernakulam.

The study was planned for detecting difference of 15 percent in the outcome variables between the two groups and Standard deviation of 156.00, with 90% statistical power and 5% level of significance, the sample size was calculated to be 70 for the study.

The study subjects were randomly assigned into 2 groups of 35 patients each.

Group 1: Patients treated with Tablet Mifepristone 25mg once daily for 3 months.

Group 2: Patients treated with Inj. Leuprolide acetate depot

preparation 3.75mg IM once a month for 3 months
Demographic data, history, clinical examination, details of drug prescription, laboratory investigations and imaging reports were recorded in the study proforma.

Clinical assessment parameters

- Menstrual Blood Loss was assessed using PBAC-Pictorial Blood Loss Assessment Chart. PBAC is a semi-quantitative assessment that analyses the number of pads soaked, their extent of soakage, passage of clots and episodes of flooding. A score of 100 or more is taken as menorrhagia.
- Dysmenorrhea, pelvic pain and backache were assessed by Visual Analog Scale for Pain.. Pain is assessed using Visual Analog Scale (VAS) score, where patients are asked to describe their pain before and after the treatment, on a scale of 0 to 10, with "no pain" taken as zero and "worst possible pain" as 10.

Laboratory and imaging assessment parameters:

- Pelvic USG to assess the uterine volume and myoma volume at enrollment and at the end of three months.
- Laboratory investigations: Hemoglobin and Hematocrit were measured in the Hematology Laboratory of SNIMS.

Statistical analysis:

The Statistical software namely SPSS 18.0 was used for assessment of data. Student t test (two tailed, dependent) was used to find the significance of study parameters on continuous scale within each group. Chi-square/ Fisher Exact test was used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis.

Results

The mean age of the pooled patient population was 44 years which compared well with that of the individual groups. [Table 2] suggests significant (p value <0.001) decrease in mean uterine volume after three months of treatment in both the groups. The effects were found to be comparable. The reduction in the mean uterine volume was 28.46% with mifepristone and 32.31% with leuprolide after 3 months. [Table 3] suggests significant reduction (p <0.001) in mean myoma volume after three months of treatment in both the groups. The percentage decrease in myoma volume was 46.5% with leuprolide as compared to 35.5% with mifepristone after 3 months. Mean endometrial thickness significantly (p < 0.05) increased from 6.3mm to 7.8mm in mifepristone group. However there was no much difference observed in leuprolide group after 3 months of treatment. [Table 4] suggests 24 patients (68.57%) in group 1 and 22 patients (62.85%) presented with dysmenorrhea. After three months of treatment, there was a marked relief with significant decrease in visual analog scale score in both the groups (p <0.001).22 patients (62.85%) in group 1 and 24 patients (68.57%) presented with pelvic pain. After three months of treatment, there was a marked relief with significant decrease in visual analog scale score in both the groups (p <0.001).24 patients (68.57%) in group 1 and 29 patients (82.85%) in group 2 presented with backache. After three months of treatment, there was a marked relief with significant decrease in visual analog scale score in both the groups (p <0.001). 21 patients (60%) in group 1 and 25 patients (71%) in group 2 presented with mild anemia at the beginning of the study. After three months of treatment, there was a significant (p <0.001) rise in the hemoglobin and hematocritvalues in both the groups. There was an increase in mean hemoglobin level by 2.9gm/dl in mifepristone group and 3gm/dl in leuprolide group.

Table 1: Age distribution of patients studied

Age in years	Mifepristone	Leuprolide	Total
35-40	12(34.3%)	7(20%)	19(27.1%)
41-45	22(62.9%)	26(74.3%)	48(68.6%)
45-50	1(2.9%)	2(5.7%)	3(4.3%)
Total	35(100%)	35(100%)	70(100%)
Mean ± SD	43.97±4.95	44.17±4.89	44.07±4.89

Table 2: Comparison of Mean uterine volume in two groups of patients

Mean Uterine Volume	Mifepristone	Leuprolide	P value
Baseline	334.38±162.18	361.06±161.46	0.082
3 months	239.21±130.54	244.37±122.63	0.064
Difference	95.175	116.686	-
P value	<0.001	<0.001	-

Table 3: Comparison of Mean myoma volume in two groups of patients studied at baseline and at 3 months

Mean Myoma volume	Mifepristone	Leuprolide	P value
Baseline	89.60±53.31	94.09±58.69	0.079
3 months	57.81±29.85	50.33±32.13	0.048
Difference	31.787	43.759	-
P value	<0.001	<0.001	-

Table 4: Comparison of dysmenorrhea in two groups of patients studied at baseline and at 3 months

Dysmenorrhea	Mifepristone	Leuprolide	P value
Baseline	4.03±2.96	3.91±2.65	0.101
3 months	0.23±0.43	0.29±0.46	0.591
Difference	3.800	3.629	-
P value	<0.001	<0.001	-

Table 5: Comparison of backache in two groups of patients studied at baseline and at 3 months

Backache	Mifepristone	Leuprolide	P value
Baseline	4.34±2.74	5.06±2.58	0.09
3 months	0.34±0.64	0.77±0.65	0.07
Difference	4.000	4.286	-
P value	<0.001	<0.001	-

Table 6: Comparison of Hemoglobin in two groups of patients studied at baseline and at 3 months

Hemoglobin (g/dl)	Mifepristone	Leuprolide	P value
Baseline	8.31±1.68	8.26±1.55	0.894
3 months	11.17±1.28	11.36±1.22	0.530
Difference	-2.857	-3.097	-
P value	<0.001	<0.001	-

Discussion

Leiomyoma being a hormone dependent tumour, stops to grow after menopause. Therefore hormonal treatment reduces size, improves hemoglobin by controlling bleeding and surgery may be avoided if patient is nearing menopause.[6] The results of our study revealed that the reduction in uterine volume was 32.3% with Leuprolide and 28.5% with mifepristone. Previous studies conducted either with mifepristone or leuprolide have shown similar reduction in uterine volume.[7-9] According to our comparative study, the reduction in uterine volume with mifepristone was comparable to that produced by leuprolide.

The reduction in myoma volume with Leuprolide was 46.4% after three months of treatment. Several studies have reported reduction in myoma volume with GnRH agonists.[9] The median rate of myoma volume reduction with GnRH agonist therapy reportedly ranges from 42% to 58.3%.[10,11] Evidences suggest that oestrogens and progestogens play a major role in myoma growth. It is well established that myoma growth occurs only in premenopausal women, and this growth is diminished in hypo oestrogenic states such as menopause or during GnRH agonist therapy.[12]

Progesterone is equally essential for maintenance and growth of uterine leiomyoma and also estrogen up regulates progesterone receptors.[13] Reduction in size with mifepristone might be due to the direct effect in reducing number of progesterone receptors. Mifepristone due to its antiglucocorticoid effect may also inhibit steroid dependent growth of myoma. Up regulation of androgen receptors may also contribute to its anti-proliferative effects.[11-13] The reduction in myoma volume attained after 3 months of treatment with oral mifepristone 25mg was 35.5% in our study. Studies have evaluated mifepristone in varying doses from 2.5 to 50 mg/day given for 3 to 6 months and results have revealed reduction in myoma volume by 26-57 per cent.[8,14,15]

Excessive menstrual bleeding is often the most common symptom reported by women with leiomyomas.16 Abnormal uterine bleeding or menorrhagia was the most common symptom for which the patients in our study sought medical advice like in other studies.[6,7] 53 out of the 70 patients had menorrhagia, along with other symptoms. Menstrual blood loss was assessed using pictorial blood loss assessment chart (PBAC) scores.[17-19] Twenty three patients (65.7%) in group I (Mifepristone) and Twenty five patients (71.4%) in group II (Leuprolide) developed amenorrhea after 3 months while others had only minimal menstrual blood loss. Reduction in menstrual blood loss attained using both drugs were similar. The mean PBAC score reduced from 110 to 10 after three months of treatment with mifepristone and in leuprolide group, the mean PBAC score reduced from 118 to 9.

Dysmenorrhea, pelvic pain and low backache were evaluated in our study. Common causes of secondary dysmenorrhea include endometriosis, fibroids (myomas), adenomyosis, endometrial polyps, pelvic inflammatory disease, and use of intrauterine contraceptive device. Studies have identified that production of uterine prostaglandins is one reason for dysmenorrhea.[20]

Endometrial thickness may be variable from individual to individual. In our study, the mean endometrial thickness increased from 6.3mm to 7.8mm in mifepristone group after 3 months of treatment, which was significant ($p < 0.05$). There was no much increase in endometrial thickness in leuprolide group after 3 months. Endometrial hyperplasia was a concern in almost all previous studies involving low dose mifepristone.[14-18] In our study, we observed that treatment with mifepristone 25mg daily for three months significantly reduced bleeding, uterine volume and myoma volume in symptomatic cases and improved the quality of life. The drug was well tolerated by the women as evidenced by no dropouts. There were no major side effects too. Mifepristone may reduce further growth of myomas in symptomatic perimenopausal women who wish to avoid surgery. In the present study, we observed that GnRH agonist Leuprolide was effective in inducing a consistent hypo-estrogenic state and subsequent shrinkage of myoma. Reduction in myoma volume is presumed to be due to the induction and maintenance of the hypo-estrogenic state.

Conclusion

Treatment with either mifepristone or leuprolide acetate in uterine leiomyoma is safe and causes significant but temporary reductions in uterine size and myoma related symptoms. Further studies are required to establish the efficacy and safety of more prolonged treatment with both mifepristone and leuprolide.

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