Comparing the Outcome of Ullipristal Acetate and Mifepristone in the Medical Management of Uterine Fibroids

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Abstract: _Introduction: Uterine leiomyomas are widely prevalent and frequently cause menorrhagia. The major therapeutic option today is hysterectomy. Medical options are of highest interest. Aim & Objectives: Efficacy and safety of mifepristone in medical management of myoma and to compare two doses - 10 vs. 25 mg/day versus ullipristal acetate 5mg/day. Materials & Methods: study period from January 2016 to january 2018.A total of 150 women with uterine leiomyomas randomized to receive 10mg, 25 mg mifepristone Group 1: Patients were randomized and were given oral mifepristone as 25 mg/day in group 1 for 3 months Group 2: oral mifepristone 10 mg/day in group 2 for 3 months. GROUP 3: Patient s were randomized and given ullipristal acetate 5mg/day for 3 months All Patients were followed at 1, 3 and 6 months. Haemogram, liver function test, ultrasound with doppler and endometrial histology was performed.. Uterine blood flow and leiomyoma volume were evaluated Endometrial biopsies were obtained prior to and at end of treatment. Relevant biochemistry, symptoms and bleeding were recorded. Primary outcome was reduction in uterine leiomyoma size. Results: There was a significant decrease in the total leiomyoma volume in the mifepristone-treated group, Mifepristone treatment significantly reduced the bleeding days and increased serum haemoglobin values. Serum cortisol levels remained unchanged, while a mild increase in serum androgens was noted. Endometrial biopsies showed no premalignant changes or changes in mitotic indices. 1. Comparing the fibroid size in volume between three groups ANOVA test results in a statistically significant difference between the three groups with P-value less than 0.05. Post-hoc tests confirm that there is statistically significant difference between i. Group 1 & Group 2; An average reduction of fibroid size by 51% more in Group 1 as compared to Group 2 ii. Group 1 & Group 3; An average reduction of fibroid size by 74% more in Group 1 as compared to Group 3 Patients on ullipristal acetate showed minimal reduction of fibroid with menorrhagia or spotting during the treatment with 10 patients with deranged liver function test. Conclusion: Mifepristone offers an effective treatment option for women with uterine leiomyoma and the associated pronounced uterovaginal bleeding._

Keywords: Ullipristal Acetate, Mifepristone, Fibroids

1. Introduction

Fibroids are the most common tumour of women during reproductive life. They are symptomatic in 50% of women who have them, with the peak incidence of symptoms occurring among women in their 30s and 40s [1]. Symptoms include menstrual disturbance (commonly menorrhagia pressure symptoms like increased frequency of urine, pelvic pain, constipation. Thus although benign, fibroids have a major impact on women's health and their quality of life. Current treatment options for the woman with symptomatic fibroids include abdominal hysterectomy, conventional abdominal myomectomy, laparoscopic and vaginal myomectomy [3,4] and the radiological interventions uterine artery embolisation (UAE)] and magnetic resonance-guided focused ultrasound surgery (MRgFUS) [6]. Hysterectomy is unacceptable to the woman wishing to retain fertility potential, while conventional myomectomy is associated with risks of adhesions, morbidity and indeed mortality. Both laparoscopic and vaginal myomectomy require skills that are not commonplace and there are limitations on the size and number of fibroids that can be treated by these modalities.Current medical therapeutic approaches exploit the observations that uterine fibroids s have significantly increased concentration of estrogen and progesterone in the myometrium compared to normal myometrium and that ovarian steroids influence fibroid growth.

Gonadotrophin-releasing hormone and while they do cause fibroid regression, they can only be used in the short term, as temporising measures in the perimenopausal woman. They are notorious for rebound growth of the fibroids upon cessation of therapy and have major side-effects. Its

physiological effects impact the processes of endometrial differentiation, ovulation, implantation, successful development of the embryo, development of the mammary gland and regulation of central signals from the hypothalamic–pituitary (HP) axis.

The effects of progesterone on target tissues are mediated via the progesterone receptor (PR), which belongs to the nuclear receptor family [11]. The PR exists as three separate isoforms (A, B and C) expressed from a single gene [11]. PR antagonists oppose the biological actions of progesterone by inhibiting PR activation. Progesterone has dual actions on fibroid growth. It stimulates growth by up-regulating EGF and Bcl-2 and down-regulating tumor necrosis factor-alpha expression while it inhibits growth by down-regulating IGF-I expression [12,13].

While it has long been established that estrogen promotes fibroid growth, recent biochemical and clinical studies have suggested that progesterone and the PR may also enhance proliferative activity in fibroids. These observations have therefore raised the possibility that anti-progestins and agents or molecules that modulate the activity of the PR could be useful in the medical management of uterine fibroids. Since the emergence of mifepristone (RU-486), the first PR antagonist more than 25 years ago, hundreds of steroidal as well as nonsteroidal compounds displaying progesterone antagonist (PA) or mixed agonist/antagonist activity have been synthesised. Since the emergence of mifepristone (RU-486), the first PR antagonist, more than 25 years ago, hundreds of steroidal as well as non-steroidal compounds displaying progesterone antagonist (PA) or mixed agonist/antagonist activity have been synthesised. Collectively, they are known as progesterone receptor

modulators (PRMs). These compounds have a huge potential for use in the treatment of a number of pathological conditions of the female reproductive system including uterine fibroids, endometriosis and dysfunctional uterine bleeding and as potential contraceptives. Some of the PRMs which have been the subject of recent clinical trials or research studies in relation to fibroid treatment include emifepristone, CDB-4124CP-8947 and J867 (asoprisnil) and CDB-2914 (ulipristalacetate).

Progesterone receptor modulators (PRMs). Mechanisms of action. The following mechanisms of action have been proposed

(a) Ulipristal down-regulates the expression of angiogenic growth factors such as vascular endothelial growth factor (VEGF) and their receptors in cultured fibroid cells [23] resulting in suppression of neovascularisation, cell proliferation and survival Ulipristal and asoprisnil inhibit proliferation of cultured fibroid cells and induce apoptosis by up-regulating cleaved caspase 3 and down regulating Bcl-2 [] Ulipristal also increases the expression of matrix metalloproteinases and decreases the expression of tissue inhibitor of metalloproteinases. Asoprisnil and ulipristal have been shown to modulate the ratio of progesterone receptor isoforms (PR-A and PR-B) in cultured leiomyoma cells [24][25]. They decreased the cell viability; suppressed the expression of growth factors, angiogenic factors and their receptors in those cells; and induced apoptosis by activating the mitochondrial and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) pathways and eliciting endoplasmic reticulum stress. there was little evidence of mitosis, consistent with the anti-proliferative effect of PRMs. No biopsy demonstrated atypical hyperplasia [26] [27].There was asymmetry of stromal and epithelial growth and prominent cystically dilated glands with both admixed estrogen(mitotic) and progestin (secretory) epithelial effects. This histology has not previously been encountered in clinical practice

2. Material and Methods

This prospective randomized clinical trial was conducted from January 2016 to january 2018, at the Department of Obstetrics and Gynaecology, at Aster Medcity Cochin, India, after obtaining ethical clearance from the Institute's Ethics Committee. Inclusion criterion Women between 20-50 yr of age with single or multiple fibroids, if they were symptomatic or if the largest fibroid was >5 cm on ultrasound. Ultrasound pelvis was done for all patients to exclude any other obvious causes like adenomyosis, endometriosis, adnexal mass for the above symptoms. Exclusion criteria remained more than 20 week gravid size uterus, fibroids >15 cm by ultrasound, grade-0 submucosal fibroids, renal or hepatic dysfunction, suspected adenomyosis, current genital infection, endometrial hyperplasia with atypia and hormonal medication within 3 months and women desiring pregnancy. clinical details of menstrual cycle, symptoms and their severity was noted. Menstrual blood loss was assessed by pictorial blood loss assessment chart (PBAC) that takes into account the number of pads soaked, their degree of soakage, passage of clots. Visual analog scale (VAS) score was noted for pain,

dysmenorrhoea, dyspareunia, pelvic pain and pressure symptoms, where patients were asked to describe their pain on a scale of 0 to 10, before and after the treatment, with "no pain" taken at zero and "worst possible pain" at 10.

A complete examination was done. Blood testing was done for haemoglobin, liver and kidney function tests. Ultrasound was done to confirm the diagnosis of leiomyomas as well as to ascertain number, site, volume of myomas, to measure endometrial thickness and to rule out any other pelvic pathology. Volume of each myoma was calculated and added in cases with multiple myomas. Fibroid volume was calculated by the ellipsoid method and the formula $V=0.5233(D1 \times D2 \times D3)$ was used, where D1, D2 and D3 are the longitudinal, transverse and cross-sectional diameters of the fibroid, respectively. In multiple myomas, volumes of all myomas were added.Endometrial aspiration was performed to rule out any abnormality. the sample size for each group was calculated to be 75 patients. Hence, 225 women with inclusion criteria were recruited in the study after taking informed written consent. Patients were randomized into three groups according to computerized randomization. Mifepristone was given as 25 mg/day in group 1 and as 10 mg/day in group 2, starting initially from day 2-3 of periods.group 3 were given ullipristal acetate 5 mg daily. Duration of treatment was 3 months.

Since mifepristone is available in India as 10 and 25 mg were given to the patients and ullipristal acetate 5mg given. Patients were followed up at 1 and 3 months while on therapy and then at 6 months on each visit clinical symptoms including bleeding and spotting, PBAC score, VAS score and any side effects were assessed.

At 3 months follow up; haemoglobin, liver function test, renal function test were repeated. Ultrasound with uterine artery Repeat endometrial aspiration was done after completing 3 months of treatment.
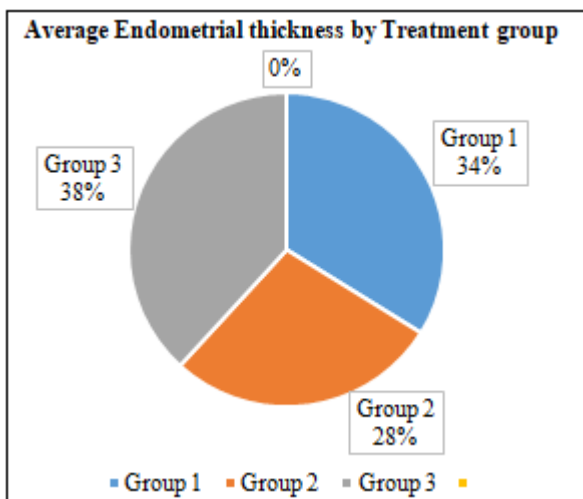
3. Results
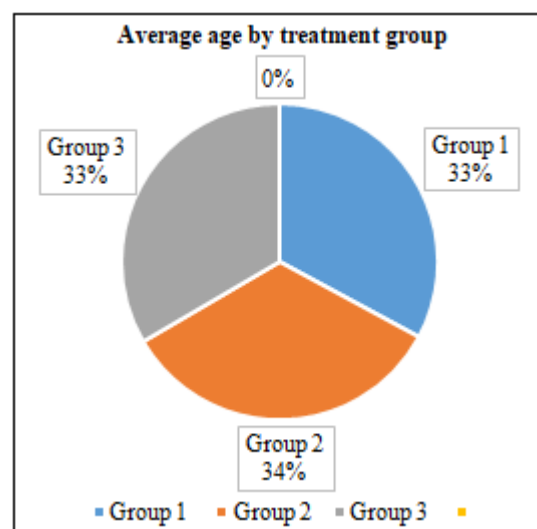
Mean age is almost similar in all the groups with 42 years

Average reduction in fibroid size by treatment group
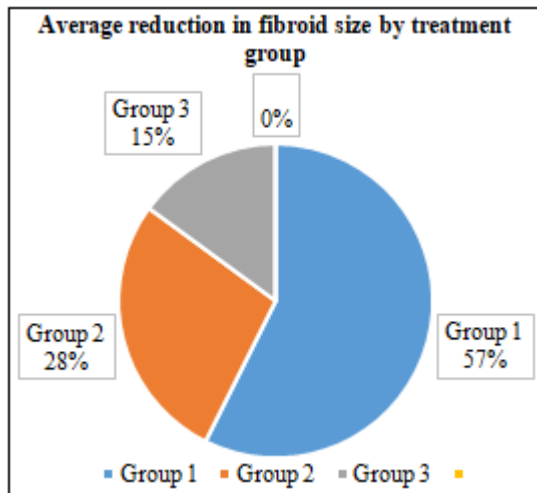
Group 1 has maximum reduction in average Fibroid size compared to Group 2 and Group 3 with a volume of 97 as compared to Group 2 with 47 and Group 3 with 25

Average Endometrial thickness by Treatment group

Highest endometrial thickness post intervention is in Group 3 with an average thickness of 10 as compared to 7.6mm in Group 2 and 9mm in Group 1
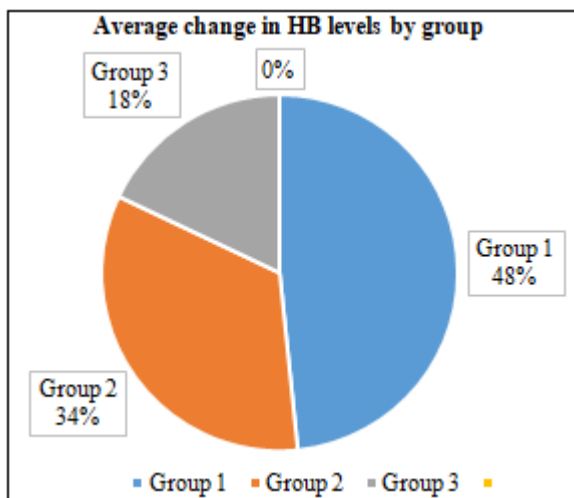
Average change in HB levels by group

Maximum change in HB level was observed in Group 1 with an average absolute difference of 1.06 as compared to Group 2 with 0.7 and Group 3 with 0.3

Table 1

Symptoms	Group 1	Group 2	Group 3
Asymptomatic	7%	0%	4%
Backache	9%	26%	18%
Dysmenorrhea	17%	18%	35%
Dyspareunia	0%	2%	0%
Menorhagia	63%	52%	43%
Pain lower abdomen	2%	2%	0%
Spotting p/v	2%	0%	0%

E.g. Group 2 had the maximum amount of patients with symptoms of backache with 26% whereas only 18% had backache in group 3 and 9% in Group 1

Table 2: Percentage distribution of Histopathology by Groups

Histopathology	Group 1	Group 2	Group 3
Decidualised stroma	0.0%	4.0%	8.2%
EHWA	8.7%	0.0%	16.3%
Inadequate	0.0%	2.0%	0.0%
Menorrhagia	0.0%	0.0%	2.0%
Proliferative	50.0%	78.0%	55.1%
Secretory	41.3%	16.0%	18.4%

E.g. 78% of patients in Group 2 had Proliferative histopathology whereas Group 3 had 55% patients with proliferative histopathology and least patients was observed in Group 1 with 50%.
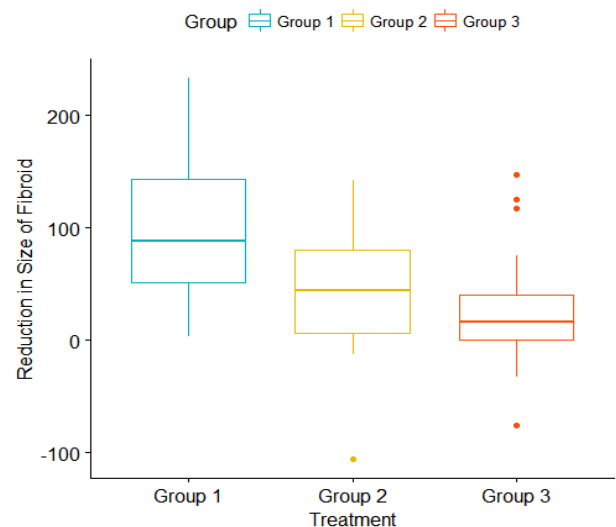
Comparisons
1) Comparing the fibroid size in volume between three groups

ANOVA test results in a statistically significant difference between the three groups with P-value less than 0.05. Post-hoc tests confirms that there is statistically significant difference between
a) Group 1 & Group 2; An average reduction of fibroid size by 51% more in Group 1 as compared to Group 2
b) Group 1 & Group 3; An average reduction of fibroid size by 74% more in Group 1 as compared to Group 3

There is no observed statistically significant difference between Group 2 and Group 3 in terms of reduction in Fibroid size.
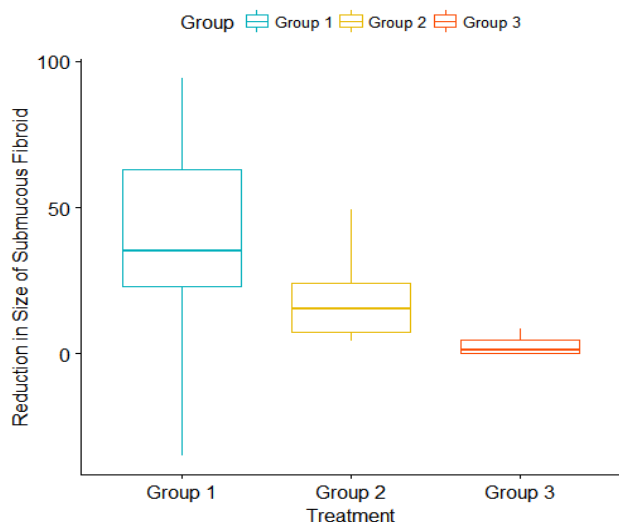

2) Comparing the submucous fibroid volume in size between three groups

ANOVA test results in a statistically significant difference between the three groups with P-value less than 0.05. Post-hoc tests confirms that there is statistically significant difference between

Group 1 & Group 3; Average reduction of submucous fibroid size by 93% more in Group 1 as compared to Group 3

There is no observed statistically significant difference between Group 2 and Group 3 or Group 1 and Group 2 in terms of reduction in submucous Fibroid size.

3) Comparing the fibroid size in volume between 25mg and 10mg
   T test results in a statistically significant difference between the two groups with P-value less than 0.05. We observe an average reduction of fibroid size by 51% more in Group 1 as compared to Group 2
4) Group 3 10 patients had deranged liver function test.

4. Conclusion

Maximum change in HB level was observed in Group 1 with an average absolute difference of 1.06 as compared to Group 2 with 0.7 and Group 3 with 0.3

Group 1 & Group 3; Average reduction of submucous fibroid size by 93% more in Group 1 as compared to Group 3

There is no observed statistically significant difference between Group 2 and Group 3 or Group 1 and Group 2 in terms of reduction in submucous Fibroid size.

Comparing the fibroid size in volume between 25mg and 10mg

T test results in a statistically significant difference between the two groups with P-value less than 0.05. We observe an average reduction of fibroid size by 51% more in Group 1 as compared to Group 2

Group 3 showed deranged liver function test in 10 patients compared to 1 patient in group 1

5. Conflicts of Interest

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