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Ulipristal in Fibroids

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Abstract
Symptomatic uterine fibroids are managed by surgery. The medical management involves Tranexamic acid, OC pills, Progesterone, LNG IUS, GnRH analogues, as a temporary measure pre operatively. Selective Progesterone Receptor Modulators (SPRMs) are new group of drugs for the medical management. Ulipristal acetate is a SPRM, clinically approved drug in the management of fibroids.
The study was conducted at a tertiary care hospital in South India. Fifty women with fibroids and menorrhagia, awaiting definitive surgery or pre-operative to make them fit for surgery or wants medical treatment- are the subjects of the study. At the initiation of the treatment blood loss was quantified by PBAC scale. The number and volume of the fibroids were assessed by ultrasonography. Associated symptoms were recorded. Urlipristal acetate 5 mg daily was given for three months. Blood loss, amenorrhoea, and volume of fibroids was assessed at three months of treatment. Side effects were recorded. They were followed for further three months for resumption of menses.
The mean blood loss was reduced by 88 %. Eighty two percent of women had amenorrhoea. There was 28.2 % of reduction in the volume of the fibroids. There were no troublesome side effects. Two amenorrhic women had hot flushes. 47 resumed menses in 30-40 days and the bleeding was normal or slightly less. There was relief from dysmenorrhoea and pressure symptoms of fibroids
The results of the study were compared with those of other studies. In terms of control of menorrhagia and reduction of fibroid size, 5 mg dose of ulipristalis equally efficacious as 10 mg dose.
Keywords: *Symptomatic Fibroids; Menorrhagia; Ulipristal acetate; SPRMs.*

Introduction

Leiomyoma is the most common benign pelvic tumour in the reproductive age group women. At ultrasonographic examination, fibroids including the smallest ones are seen in 80% of women. Three fourths of fibroids are asymptomatic. The symptoms of fibroids are--menorrhagia with resultant anemia; dysmenorrhoea; pressure symptoms like urinary problems and discomfort in abdomen and pelvis; infertility. Sarcomatous change is extremely rare. Asymptomatic fibroids don`t warrant any treatment. Symptomatic fibroids are managed--surgically by Polypectomy, Myomectomy or Hysterectomy; radiologically by Uterine Artery Embolization, Magnetic Resonance guided Focussed Ultrasound

(MRgFUS), Laparoscopic ,Ultrasound guided Radio Frequency Ablation of fibroids; medical management is by Non steroidal Anti inflammatory drugs, Tranamexic acid; Hormonal interventions like Oral Contraceptives (OC Pills), Progesterones, Gonadotrophin Releasing Hormone analogues (GnRHa), Levonorgestrel Releasing Intrauterine Systems (LNG IUS). In the past decade, Selective Progesterone Receptor Modulators (SPRMs) evolved as a new method of medical management of fibroids. This is used to alleviate the symptoms of fibroids, preoperatively to prepare the patient for surgery, to reduce the size of the fibroids.

Fibroid growth is Estrogen dependent. Progesterone and progesterone receptors are required for fibroid cellular proliferation. It is observed that, progesterone and progesterone receptors PR A, PR B are elevated in the leiomyoma. SPRMs by acting on PR A, PR B cause antiproliferative and proapoptotic effects on leiomyoma. SPRMs inhibit Pituitary release of Leutinising Hormone (LH) resulting in anovulation and amenorrhoea.

Mifepristone, Asoprisnil, Ulipristal acetate are the clinically useful SPRMs. Ulipristal is the approved SPRMs for the management of fibroids. Ten mg. of Ulipristal is given daily for three months.

PEARL 1 and PEARL 2 studies established the efficacy of Ulipristalon par with Leuprolide acetate. VENUS 1 study endorsed the findings of PEARL study in select populations. A single course of 10 mg Ulipristal daily for three months is the treatment schedule adopted in PEARL 1 and PEARL 2 studies. As an extension, PEARL 3 studied four such courses of thee months each with one menstruation intervening between the three months courses. It was found to be effective and safe. PEARL 4 aimed at eight courses of three months. PEARL 3, PEARL 4 and VENUS 2 established the efficacy and safety of Ulipristal in the management of symptomatic fibroids on a long term.

Aims

To evaluate the efficacy of 5 mg dose of Ulipristal in the management of menorrhagia in fibroids and to evaluate the reduction in the size of the fibroids in a single three months course.

Material and Methods

The study was conducted in the outpatient department of Obstetrics & Gynaecology at a rural based tertiary care hospital in South India, during October 2017 - March 2019. Women with menorrhagia and fibroids in 20-45 years age group are the subjects of study. Ethical clearance from the ethical committee of the hospital was obtained. Women who are willing for the medical management of the fibroids-- women who are having both menorrhagia and fibroids—women anxious to conceive, not willing for myomectomy or awaiting myomectomy; women who completed child bearing, not willing for hysterectomy or awaiting hysterectomy were enrolled for study. Women with uterus greater than 12 weeks pregnancy size; with fibroid greater than 10 cms. in size; with endometrial hyperplasia; who had hormonal treatment in the past three months were excluded from the study. Barrier contraception was advised for non-sterilised women.

General history, reproductive history, symptomatology of fibroids, treatment history was recorded. General examination, thorough gynaecological examination was done. Routine investigations done. Ultrasonographic examination was done. Menorrhagia was assessed quantitatively by Pictorial Blood Assessment Chart (PBAC) scale. At USG examination--any other pelvic pathology; endometrial thickness; fibroids more than one cm were taken into account. The number, location, size of all the fibroids were recorded. Volume of the fibroids was measured by the formula 0.52 multiplied by ABC, ABC being the largest measurements of fibroids in three planes of A) height, B)width and C)depth. In multiple fibroids, the largest three fibroids are taken into consideration. Associated

symptoms of fibroids like dysmenorrhoea and pressure effects are recorded.

Each woman was given 5 mg. of Ulipristal daily for three months starting while on bleeding or any day of menses. PBAC was maintained for three months. After thirteen weeks of usage of the drug the woman was reassessed. She subjectively evaluated the menorrhagia, dysmenorrhoea, pressure symptoms, quality of life and satisfaction about the treatment. The woman was examined clinically and routine investigations were done. Bleeding was assessed objectively by PBAC score. PBAC < 2 was taken as amenorrhoea. PBAC< 75 was taken as nonmenorrhagia. USG was done by the same consultant for the volume of the fibroids, endometrial thickness.

The results of the initial evaluation and evaluation after three months of treatment were compared. Side effects were recorded.

The women were followed for further three months after the completion of the course for resumption of menses and amount of bleeding.

Results

Sixty three women who fulfilled the criteria were recruited for study. Five opted for surgery, eight lost for follow up after the start of treatment or has irregular course of treatment. Fifty women who completed the course as per protocol were included in the evaluation of the study.

Table 1 Age group

Age	Number	Percentage
21-25	2	4
26-30	11	22
31-35	10	20
36-40	18	36
41-45	9	18

Of the 50 women, two were unmarried, four were divorced or widowed, 44 were living with husband. 36 were sterilised, two are on barrier contraceptives, six were infertile, four wanted to have some more children.

All the 50 women had menorrhagia, eleven had severe dysmenorrhoea, 16 had one or more associated pressure symptoms. Three had endometriosis, two had ovarian pathology.

Of the 50 women, 18 had single fibroid, 20 had two fibroids, 12 had three or more fibroids, making the total number of fibroids 108. In the women with more than three fibroids, only the largest three fibroids are taken into the study, making the total number of fibroids for follow up 96.

Table 2 Location of fibroid

Location of fibroid	number	Largest three	Percentage
Intramural	76	65	68
Submucosal	3	3	3
Subserosal	6	6	6
Submucosal, intramural	9	10	10
Intramural, subserosal	14	12	13
Total	108	96	100

Before treatment the volume of the fibroids ranged from 5.5 cc to 261 cc.

The mean volume of the 96 fibroids in 50 women was 38.94 cc. before treatment. The volume is reduced to 27.96 cc after treatment. The reduction in volume of fibroids is 28.2 %.

The highest PBAC score at the start of treatment was 271. The mean PBAC score of the 50 women at the start of treatment was 158.4. At the end of the treatment, 41 women (82%) had amenorrhoea, 9 women (18%) had scanty menses. the mean PBAC score was 18.6 at three months of treatment. The reduction in bleeding was by 88%.

Of the 11 women who had severe dysmenorrhoea, only two had menses and it was with minimal pain. Of the 16 women who had pressure symptoms before treatment, the symptoms became less in 13 women. Haemoglobin rose by 3.1 gms. in the three months of treatment.

Head ache, nausea, abdominal pain, breast tenderness mentioned as the side effects of Ulipristal are not bothersome in any of the women treated. One woman had hot flushes.

Discussion

The utility of Ulipristal in the management of menorrhagia and in reducing the size of fibroids was well documented in PEARL I and PEARL 1 studies. In the present study, the reduction in menorrhagia, amenorrhoea, reduction in the size

of the fibroids was 88%, 82%, 28.2 % respectively. This compares well with the PEARL study which showed 91.5%, 25% reduction in blood loss and fibroid volume respectively and amenorrhoea in 70%.Surendra et al. reported reduction in blood loss by 89% after using Ulipristal in 10 mg doses. Geetha Rani et al. reported reduction in menorrhagia by 75% and reduction in size of fibroid by 30%. The present study, with the usage of 5 mg of Ulipristal, almost the same clinical effect was achieved. Donnez et al. reported bleeding reduction, amenorrhoea and volume reduction of fibroids in 91%, 73%,21% of women using a single three months course of 5 mg of Ulipristal respectively, compared to 92%, 82%, 12% respectively for women using 10 mg of Ulipristal. The present study achieves similar success by using 5 mg of Ulipristal.

Conclusions

Ulipristal, a SPRM drug is useful in the medical management of symptomatic fibroids. With daily treatment for three months, a reduction in blood loss of 80-90%, amenorrhoea in 70-75% and reduction in the volume of fibroid of 20-30% can be achieved. There is no significant difference in the efficacy with 10 mg dose and 5 mg dose of Ulipristal. A dose of 5 mg can be recommended in all women instead of 10 mg dose. There are no significant bothersome side effects. Further studies are needed in hot flushes in amenorrhoic women. Studies on repeat usage of the three months courses, 4, 8 or even more such courses for long term usage of the drug may help to avoid surgery for fibroids.

Conflict of Interest: Nil

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