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Comparative Study of Effectiveness of Oral Mifepristone and Cabergoline in the Medical Management of Leiomyoma of Uterus

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ABSTRACT: The most prevalent benign tumor in the uterus, especially in fertile women, is a leiomyoma. It may remain asymptomatic or may have menstrual bleeding disorders, pain, heaviness etc symptoms. It is one of the most common gynecological problems faced in clinical practice. Surgical management though is the mainstay of treatment, medical and radio logical treatment are also used. In this study comparative effectiveness analysis of two commonly used oral medications - 1. Misoprostol and 2. Cabergoline in the management of leiomyoma in the reproductive age group have been done. Both of these drugs are relatively cheap and orally used. Patients have been selected from OPD of a clinic and they have been randomly prescribed oral Mifepristone 25mg daily or oral Cabergoline 0.5mg once weekly for 3 months. After completion of 3 months, they were assessed regarding the reduction of tumor size, reduction of pain, and reduction of menstrual blood loss. After analysis of the data, it is found that both drugs are very much effective in reducing pain and blood loss in comparison to the reduction of tumour size. Once more, there is no statistically significant difference between these two medications' efficacies in treating leiomyoma in these age ranges. So, both of these drugs can be used effectively in medical management of leiomyoma of uterus without any significant adverse effects.

KEYWORDS: Leiomyoma, Cabergoline, Mifepristone, RU 486.

I. INTRODUCTION

Premenopausal women frequently develop uterine leiomyomas, which are pelvic tumors that can have serious health consequences [1, 2]. The most typical signs are pelvic pain and irregular uterine bleeding, yet there is little chance that these tumors will turn into cancer. Even though many women may not show any symptoms, leiomyom as can never the less bevery uncomfortable and incapacitating. Abnormal uterine bleeding, pelvic pain, frequent urination, constipation, miscarriage risk, dyspareunia (pain during exual activity), and sub fertility are among the possible symptoms of leiomyomas. These tumors have a significant role in the health problems that women experience while they are fertile. Although the precise etiology of uterine leiomyomas is unknown, a number of risk factors, such as age, race, and obesity, have been found. Their development is thought to be significantly influenced byestrogen and progesterone, which has led to a variety of medical control techniques. Studies reveal that compared to normal uterine tissue, leiomyomas contain larger numbers of progesterone and estrogen receptors [3]. Never the less, it is still unknown what initially caused these tumors to grow [4]. Research suggests that the formation of leiomyomas is stimulated by ovarian hormones, specifically progesterone and estradiol, and that these tumors often shrink in size during menopause as hormone levels fall [4]. There are a number of therapy options for women with symptomatic leiomyomas, including medical care, surgical intervention, and expectant management (particularly for those who are approaching menopause).These approaches aim to alleviate symptoms and improve quality of life. Leiomyoma treatments comein a variety of forms, such as pharmaceutical, radiologic, and surgical procedures. Nonsteroidal anti-inflammatory drugs (NSAIDs), tranexamic acid, hormonal contraceptives, GnRH analogs, anti-progesterone drugs like RU486 (mifepristone), selective progesterone receptor modulators, levonorgestrel-

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releasing intrauterine devices, selective estrogen receptor modulators (SERMs), aromatase inhibitors, danazol, and even herbal medicine have all been successfully used as medical treatments to manage symptoms [2]. These drugs do not treatleiomyomas; rather, they can assist manage symptoms. As up to 40% of all hysterectomies performed on premenopausal women are related to surgical treatment, it is still the gold standard for treating symptom aticmyomas[2].While there are non-surgical options, they are not without restrictions. Although progesterone may be just as important for sustaining and accelerating the growth of leiomyomas as estrogen has historically been thought to be for this type of tumor. Progesterone receptors must be upregulated largely by estrogen [3]. This change in knowledge has prompted more study into progesterone receptor modulators such as CDB-2914, asoprisnil, andulipristal(PEARL Study) as non-surgical treatment alternatives for uterine myomas [5, 6]. Mifepristone (RU 486) functions mainly as an antagonist of the progesterone receptor; it up regulates the androgen receptors and binds strongly to the endometrial progesterone receptors, showing little affinity for the estrogen receptors [7]. Cabergoline, a dopamine receptor agonist, and low-dose Mifepristone, an anti-progesterone, are two widely used and efficient medications. Furthermore, the pituitary gland and uterine cells both emit the hormone prolactin, which can promote the formation of myomas through both autocrine and paracrine processes.

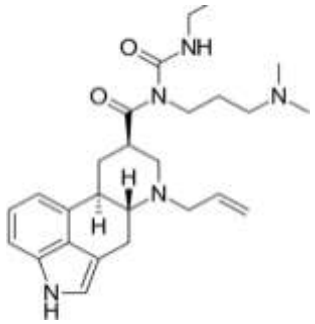

Figure1:Chemical structure of Cabergoline

A strong dopamine D2 receptor agonist derived from ergot, cabergoline was developed in 1980and given medical approval in 1993 [5, 6]. Prolactinomas, pituitary tumors that secrete prolactin, are treated with it mainly as an adjuvant therapy for hyperprolactinemia and lactation suppression. In addition, cabergolineis used as mono therapy in the early stages of Parkinson's disease and in combination with carbidopa and levodopain the later stages of the condition.Its efficacy in treating uterine leiomyomas has also been reported[7,8]. Whenused for hyperprolactinemia and other endocrine or gynecologic problems, where the normaldoseis only one-hundredth to one-tenth of that used for Parkinson's disease, the side effects of cabergoline are generally dose-dependent and regarded as minimal. Prolactin receptors have been found in the tissues of both leiomyomas and the myometrium, with various myomas exhibiting varied amounts of these receptors [9]. In these tissues, prolactin can function as a growth factor via both autocrine and paracrine pathways. Consequently, prolactin-lowering medications such as cabergoline may be used in conjunction with other therapeutic approaches to assist control myoma symptoms. One of the ways that cabergoline works the rapeutically is by preventing the release of GnRH [10]. Its usage in controlling leiomyomas has been the subject of numerous investigations, including comparative studies. In one such trial, GnRH agonists and cabergoline were examined by Elbareg et al. In this trial, 0.5mg of Cabergoline was delivered weekly for six weeks to 21 women, exhibiting comparable effects to GnRH agonists with less side effects [11, 12, 13]. In another single-blind randomized clinical trial, women with symptomatic leiomyomas were treated with 0.5 mg of cabergoline weekly for three months. This treatment significantly decreased the size of the largest myoma and the uterus, as well as the amount of menstrual bleeding. It also significantly reduced pain and other symptoms when compared to the control group [14, 15].

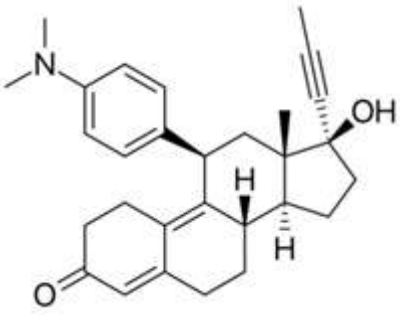

Figure2:Chemical structureod Mifepristone

In order to assist medical abortion and manage early miscarriage, mifepristone, also known by its developmental code name RU-486, is

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a drug that is frequently used in combination with misoprostol [16].It was created in 1980 and is an antiprogestogen. It was first used in France in 1987 before being made available in the US in 2000. Mifepristone has been used to treat endometriosis and symptomatic leiomyomas (uterinefibroids) in addition to its usage in reproductive health [17]. Hospitalization rates for serious problems from mifepristone range from 0.04% to 0.09%, and approximately 0.05% of cases necessitate blood transfusions [17]. Low dosages of mifepristone have been demonstrated to decrease the size of myomas and associated symptoms in a placebo-controlled trial [18]. Its direct action on reducing the number of progesterone receptors may be the cause ofthe size reduction [19]. Furthermore, it has been proposed that VEGF, or vascular endothelial growth factor, may help lower menstrual blood loss [20, 21, 22]. Murphy et al. first reported on the efficacy of mifepristone as a myoma therapy in 1993 [23, 24, 25]. It has been shown to reduce myoma volume by 26% to 57% and induce amenorrhea in 41% to100%of instances, in addition to alleviating symptoms connected tomyoma such as dysmenorrhea, menorrhagia, and pelvic pressure [19, 25, 26]. It has been shown to reduce myoma volume by 26% to 57% and induce amenorrhea in 41% to 100% of instances, in addition to alleviating symptoms connected to myoma such as dysmenorrhea, menorrhagia, and pelvic pressure [19, 25,26]. Mifepristone is generally regarded as a well- tolerated medication with no notable side effects recorded [21, 27]. The effects of cabergoline and mifepristone with alternative medical management techniques have been compared in a number of studies [7,10,14,23,28]. This study aims to conduct a comparative analysis of the efficacy of these two drugs in managing leiomyomas, focusing on reductions in bleeding, size, pain, and improvements in anemia.

II. STUDY DESIGN

Women aged 20 to 40 years with ultrasound-detected solitary or multiple leiomyomas, each measuring no more than 10 cm, were selected from the outpatient department (OPD). These patients presented with a range of symptoms, including pain, bleeding, dyspareunia, heaviness, anemia, or were symptomless. Given that leiomyomas are the most common tumors in this age group, many patients preferred medical therapy over surgery. A recent ultrasound, hemoglobin level assessment, and pain evaluation using a Visual Analog Scale(VAS),along with a thorough clinical history and examination, were conducted. Patients meeting the inclusion criteria were counseled about their management options and randomly assigned to receive either Mifepristone 25 mg daily or Cabergoline 0.5 mg weekly, starting from day one today three of their menstrual cycle for three months. In total,110 patients participated in the study, with 60 in the Mifepristone group and 67 in the Cabergoline group. Patients were asked to return to the OPD for monthly follow-up visits over three months, during which they reported their symptoms, including pain, dyspareunia, and any side effects experienced. Findings were recorded and compared. At the end of the study, after three months, ultra sonography and hemoglobin levels were reassessed. Unfortunately, 10 patients from the Mifepristone group and 7 from the Cabergoline group were lost to follow-up, resulting in 50 patients in the Mifepristone group and 60 in the Cabergoline group being evaluated. For outcome analysis, patients were divided into different groups based on their presenting symptoms and treatment outcomes after three months. Initially, 52 patients in the Mifepristone group and 61 in the Cabergoline group attended their first follow-up. Notably, none of the patients reported serious side effects, although mild nausea and dizziness were observed in the Cabergoline group. After three months, ultra sonography and hemoglobin levels were tested for each patient, and they were interviewed regarding any menstrual disorders and pain. Importantly, there was no decrease in hemoglobin levels in any of the patients.

III. RESULT ANALYSIS

In Table 1, the details of the enrolled patients are presented, showing that 50 patients received treatment with Mifepristone, while 60 patients were treated with Cabergoline. Table 2 and Table 3 illustrate the initial clinical presentations of these patients. The improvements observed after completing the study are outlined in Table 4 and Table 5. A comparative bar diagram representing these data is provided in Figure 3, along with the determined p-value, which evaluates the statistical significance of the findings.

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Table1:Enrolled patients.

Drug	Age group	No of pts	Parity	No ofpts	Total
Mifepristone	20–40	50	Nullipara	20	50
			Parous	30	
Cabergoline	20-40	60	Nullipara	30	60
			Parous	30	

Table 2
Initial presentations in Mifepristone group:

Tumouir Size		Pain			Blood Loss			A symptomatic
<5cm	5–10cm	Dysmenorrh oea	Dyspareu nia	Persistent pain	Menorrha gia	Menometrorrhagia	Normal flow	
23	27	29	22	21	27	14	09	09

Table3
Initial presentations in Cabergol in group:

Tumouir Size		Pain			BloodLoss			Asymptoma tic
<5c m	5–10c m	Dysmenorrh oea	Dyspareu nia	Persiste nt pain	Menorrha gia	Menometrorrha gia	Norm al flow	
25	35	35	28	17	28	22	12	11

Table 4Mifepristone Group:

Age	Tumouir Size decrease		Pain			Blood Loss			A symptomatic
	<5c m	5–10c m	Dysmenorrhoea	Dyspareunia	Persistent pain	Menorrhagia	Menometrorrhagia	Normal flow	
20-40	<30 % ↓- 12 >30 % ↓- 11	<30 % ↓- 11 >30 % ↓- 16	Noeffect-0 Decrease-25 Absent-4	No effect-1 Decrease-17 Absent-4	No effect-1 Decrease-17 Absent-5	No effect-3 Decrease-24	Noeffect-1 Decrease-13	09	09
% of Improvement	48	59	100	95	96	89	93		
			Average: 97%			Average: 91			

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Table 5 Cabergolin group:

Age	Tumouir Size		Pain			BloodLoss			Asymptomatic
	<5c m	5–10c m	Dysmenorrhoea	Dyspareunia	Persistent pain	Menorrhagia	Menometrorrhagia	Normal flow	
20-40	<30 % ↓- 12 >30 % ↓- 13	<30 % ↓- 18 >30 % ↓- 17	Noeffect-0 Decrease-28 Absent-7	No effect-0 Decrease-22 Absent-6	No effect-1 Decrease-12 Absent-4	No effect-2 Decrease-26	Noeffect-1 Decrease-21	12	11
% of Improvement	52	49	100	100	93	93	95		
			Average: 98%			Average: 94%			

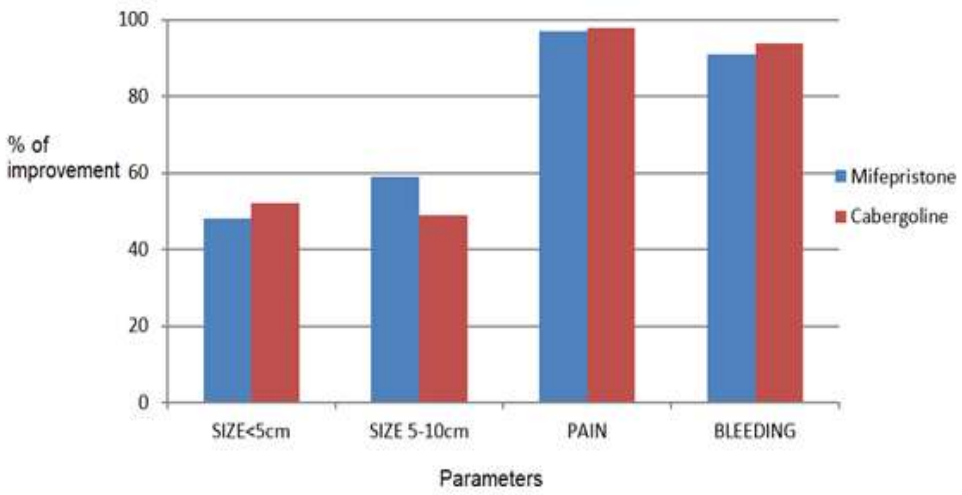

Figure3: Comparative graphical representation of the analysis

IV. DISCUSSION

After analyzing the data from both group of patients in about 50 % of patients there was more than 30% decrease in size of the tumour, which is almost comparable. on the contrary there is appreciable improvement regarding pain and menstrual blood loss. If we calculate the p-value of size reduction between two study groups it is 0.338, statistically not significant. Now if we take reduction of pain and calculate the p-value it is 0.235, it is also statistically not significant. Now finally if we take reduction in menstrual blood loss and calculate the p-value, it is 0.273, it is again statistically not significant.

V. CONCLUSION:

From this study it can be concluded that both of these two drugs are equally effective in reducing the bleeding problems and pain in patients with leiomyoma in reproductive age group women. Size of the tumours also decreased, but improvement in respect of bleeding and pain is definitely higher.

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