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ORIGINAL RESEARCH

Role of non-hormonal treatment in medical management of fibroid: An-vivo study

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ABSTRACT

Introduction: The most prevalent benign tumor of the female reproductive system, uterine fibroids (UFs) pose a serious threat to the health for women who are of reproductive age. The intervention can be hormonal or non-hormonal. Due to limited literature on the non-hormonal management of UF, there was a clear need to evaluate the effect of non-hormonal intervention in the management of symptoms commonly attributed to fibroids. **Aim and Objectives:** This study was done to evaluate the efficacy and safety of non-hormonal treatment in medical management of fibroid with the secondary objective to identify the cost-effectiveness and side effects. **Methodology**: A hospital based prospective study was done among 200 patients of symptomatic fibroid with size ≤ 6cm size. Detailed history, examination, blood investigations and baseline ultrasound examination were done. Follow-up was done at 3 months and 6 months for ultrasound, ultrasonography and whole-body check-up. The data collected was subjected to statistical analysis. **Result:** Before intervention, uterine fibroid size was approximately 5.90 which reduced significantly after 3 months and 6 months in subserous and intramural but no significant change was reported in submucous. At baseline; mean PBAC score was 153.56 which reduced to 84.91 and 61.03 after 3 and 6 months respectively with statistically significant difference ($p<0.05$). At baseline; mean VAS was 2.76 which reduced to 1.21 and 0.40 after 3 and 6 months respectively with statistically significant difference ($p<0.05$). Before intervention, uterine fibroid volume was approximately 22.5. After 3 months and 6 months of intervention, volume was reduced significantly in subserous and intramural but no significant change was reported in submucous. After intervention, fibroid size and volume was reduced by 89% and 87.5% respectively. **Conclusion:** Non-Hormonal drugs were found to be useful and effective in reducing sign and symptoms and thus general condition of the women. Tripterygium Wilfordii with vitamin D showed a promising effect as it showed a reversible inhibitory effect on ovary with minimal side effects. It was seen that it was cost effective. In this study, we have calculated sign and symptoms score and it was seen that good and mild effect was seen in 58% and 34% respectively while no effect in 8%.

Keyword: Uterine fibroid, Tripterygium Wilfordii, Vitamin D.

INTRODUCTION

The most prevalent benign tumor of the female reproductive system, uterine fibroids (UFs) pose a serios threat to the health of women of reproductive age. Significant morbidity is caused by UFs, which can also negatively impact relationships, job and daily activities.[1,2] The most significant risk factors for UFs includ race (African, American), advanced age, premenopausal status, hypertension, time since first child bearing and several food additives including soy. Other important causes are vitamin D insufficiency and obesity.[3] UF cells rely on estrogen and progesterone for their multiplication. According to recent studies, progesterone has comparatively more important role in the development of fibroids.[4] There are other critical pathways as well that cause UF growth.[5,6] These pathways could potentially be targets for potential therapeutic interventions.

Most women who have UFs either do not have any symptom at all or progressively get symptoms with time. The quantity, size and/or location of fibroids have a crucial role in determining the clinical symptoms of the condition when individual is symptomatic. Heavy monthly bleeding, dysmenorrhea, non-cyclic pain, urinary symptoms, exhaustion and constipation are among the symptoms that are frequently mentioned.[7,8] Regarding role of fibroids in infertility, there is not much evidence linking fibroids to infertility.

The course of treatment for this condition is

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influenced by the location and size of myoma together with patient's age and fertility history.[9] Current medical treatment mostly involve hormonal modifications since the tumors are hormone-dependent, originate from the reproductive phase, and are inhibited after menopause.[10] Non-hormonal medications are also recommended for the treatment of UFs due to their capacity to either enhance cellular apoptosis or limit the growth of collagen synthesis and fibroid cells.

Currently, the root of TwHF is used in medicinal applications, but its stem and leaf also have similar chemical composition and function. Due to side effects of TwHF in clinical preparations, methods to reduce toxicity and elevate the efficacy of TwHF are being researched. The most popular TwHF formulations in use is TWP, which is used in Sjogren's syndrome, kidney illness, rheumatism, Crohn's disease, skin conditions and thyroid issues. After the primary harmful components in TwHF were removed, many active compounds including Triptolide, Triptonide, Celastrol, Wilforlide A and Wilforine were extracted and added to TWP. Fibroids can also be managed surgically. But surgical intervention is costly as compared to medical treatment. In medical management, there are side effects in hormonal treatment whereas there is no side effect of non-hormonal treatment.

A lot of research has been done on the hormonal management of UF but currently, we focus on the use of non-hormonal treatment in managing fibroid. Hence, the aim of this study was to study the efficacy and safety of non-hormonal treatment in medical management of fibroid along with observing the cost-effectiveness of non-hormonal treatment, to observe how beneficial non-hormonal treatment is as compared to hormonal treatment and to observe what all side effects are bypassed by giving non-hormonal treatment for management of fibroid.

METHODOLOGY

A hospital based prospective study was conducted on the patients reporting to the OPD and IPD of Department of Obstetrics and Gynecology. All diagnosed cases of fibroid were included in this study and selected using simple random sampling. The study duration was 1 year for data collection and 6 months for analysis. The sample size was 200 on the basis of average size obtained in last 5 years.

Inclusion and exclusion criteria

Symptomatic cases of fibroid, with ≤ 6cm size, not having excess bleeding, those who received a medical trial and do not require urgent surgery were included in the study. Patients with excessive bleeding and moderate to severe anemia were excluded from the study.

Study procedure

Detailed history, examination, blood investigations and baseline ultrasound examination was done. The ultrasound examination of patients diagnosed as AUB (L) was re-evaluated. Their size, location was included. Hemogram, ultrasound, OFTT was performed. A complete general and gynecological examination was done. Blood tests were done for hemoglobin and platelet count. Ultrasonography was done to confirm the diagnosis of UF and to ascertain the number, site, volume of myoma, to measure endometrial thickness and to rule out any other pelvic pathology. All patients selected as per inclusion and exclusion criteria were evaluated and their follo-up was done at 3 months, and 6 months and ultrasound was done to see the size and volume of fibroid after the treatment. Results were then compared before and after the treatment. Ultrasonography and whole-body checkup was done at 3 months and 6 months. Data collected was tabulated in an excel sheet. The frequency of measurements per group was used for statistical analysis (SPSS 24.00 for windows, SPSS inc. Chicago, USA). Difference between two groups was determined using the Chi-square test and level of significance was set up at $p<0.05$.

RESULTS

Table 1 shows the demographic data of the study subjects. Maximum subjects were from age group of 31-40 years (64%) followed by 41-50 years (20.5%). Minimum subjects were from age group of 21-30 years (15.5%). The mean age was 37.82±96 years. Parity distribution in the subjects (Table 2) showed that 63% of the subjects in the study were nulliparous, 2nd and 3rd parity was revealed in 24.5% of the subjects while 4th and above parity was found among 12.5% of the subjects. Maximum subjects were having lower SES (44.5%) followed by upper lower SES (31%). Upper SES was observed in only 3% of the subjects (Table 3). Family history of fibroid, diabetes and cancer was revealed in 12%, 9.5% and 1.5% of the subjects respectively (Table 4). Overweight and obesity was reported among 29% and 31% of the subjects respectively (Table 5). 21% of the study subjects had hypertension (Graph 1). The most common associated hyperestrogenic condition among the study subjects was PCOS (32%). Endometrial hyperplasia and endometrial carcinoma was found in 3% and 1.5% of the study subjects respectively (Table 6).

The most common complaint among the study subjects was menorrhagia (62%) followed by dysmenorrhea (38.5%). The least common complaint was vaginal discharge reported in only 4.5% of the study subjects (Table 7). Corpous cancer syndrome (diabetes, hypertension, obesity and endometrial cancer) was revealed in 1.5% of the study subjects (Graph 2). The investigative profile among the study subjects revealed that the mean Hb (g/dl), platelet count (lakh/per microliter) and OGTT was 10.23, 1.15 and high in 23 respectively (Table 8).

Comparison of uterine fibroid size at baseline and

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after treatment showed that before intervention, UF size was approximately 5.90. After 3 months of intervention, size was reduced significantly in subserous and intramural but no significant change was reported in submucous. Similar findings were observed after 6 months (Table 9). Comparison of PBAC score showed significant difference ($p<0.05$) was observed between score at baseline, 3 months and 6 months (Table 10).

TabIe1: Demographic data of the study subjects

Age Group (in years)	N	%
21-30	31	15.5
31-40	128	64
41-50	41	20.5
TotaI	200	100
Mean±SD	37.82±6.96	

TabIe 2: Parity distribution among the study subjects

Parity	N	%
Nulliparous	126	63
2nd & 3rd Para	49	24.5
4tn & Above Para	25	12.5
Total	200	100

TabIe 3: SES among the study subjects

SES	N	%
Upper CIass	6	3
Upper MiddIe	13	6.5
Lower MiddIe	30	15
Upper Lower	62	31
Lower	89	44.5
TotaI	200	100

TabIe 4: FamiIy history among the study subjects

FamiIy History	N=200	%
Fibroid	24	12
Diabetes	19	9.5
Cancer	3	1.5
None	154	77
TotaI	200	100

TabIe 5: BMI(kg/m^2)among the study subjects

BMI(kg/m^2)	N	%
Underweight	19	9.5
NormaI	60	30
Over weight	58	29
Obese	63	31.5
TotaI	200	100

TabIe 6: Associated hyperestrogenic condition with fibroid

Condition	N=200	%
PCOS	64	32
Endometrial HyperpIasia	6	3
EndometriaI Carcinoma	3	1.5
Endometrosis	2	1
Adenomyosis	2	1
Breast Cancer	3	1.5
None	120	60
TotaI	200	100

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Table 7: Complaints among the study subjects

Complaints	N=200	%
Menorrhagia	124	62
Dysmenorrhoea	77	38.5
Infertility	18	9
Polymenorrhoea	16	8
Pain in abdomen	12	6
Vaginal Discharge	9	4.5

Table 8: Investigative profile among the study subjects(n=200)

Variables	Mean	SD
Hb (g/dl)	10.23	1.79
Platelet Count(lakh/per microliter)	1.15	0.38
OGTT	23	11.5

Table 9: Comparison of the uterine fibroid size at baseline & after treatment

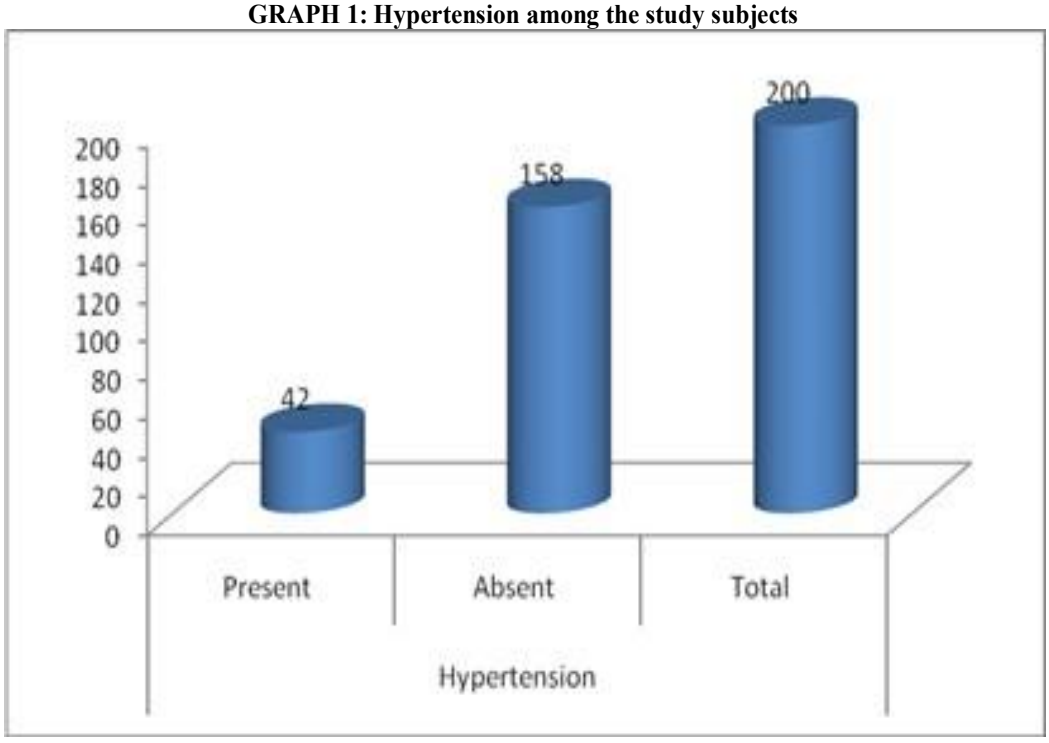
Size (cm)	Subserous		Intramural		Submucous	
	Mean	SD	Mean	SD	Mean	SD
Before Intervention	5.93	1.34	5.81	1.27	5.96	1.04
At 3months	4.88	0.37	4.95	0.52	5.83	1.16
At 6months	3.9	0.56	2.09	0.24	5.69	1.12

Table 10: Pictorial blood assessment chart (PBAC) comparison among the study subjects at different intervals

Variables	Mean PBAC	SD	p value
Before Intervention	153.56	37.82	
At 3months	84.91	29.17	
At 6months	61.03	24.65	<0.01*

*:statistically significant

GRAPH 1: Hypertension among the study subjects



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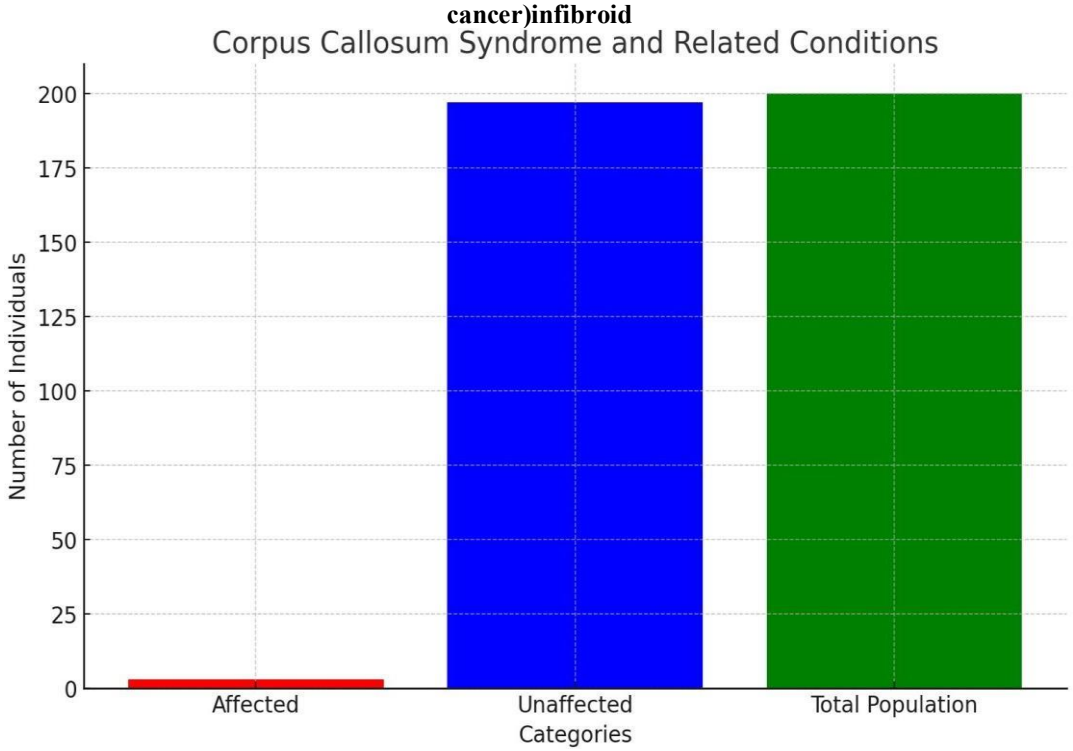
GRAPH 2: Association of corpous cancer syndrome(diabetes, hypertension, obesity, endometrial cancer)infibroid



DISCUSSION

The most prevalent benign tumor in women who are fertile is uterine myoma, sometimes referred to as fibroids. They typically decline with menopause. They are derived from the monoclonal development of smooth muscle cells in the myometrium.[11] Radical abdominal surgery should be avoided in favor of minimally invasive techniques or alternatives medical therapies for women of reproductive age. Numerous searches have been conducted regarding the hormonal management of UF, however, in this study, we concentrated on the function of non-hormonal treatment in fibroid management. The goal of this study was to compile the data in favor of non-hormonal uterine fibroid treatment while attempting to address the persistent queries about their efficacy in treating symptoms that are frequently associated with fibroids.

A hospital based prospective study was conducted in OPD and IPD of the department of Obstetrics and Gynecology among 200 cases of symptomatic fibroid with size ≤ 6cm size.

The largest group of participants (64%) belonged to the age category of 31-40 years, followed by 20.5% in 41-50 years, 15.5% of the minimum subjects were in the age range of 21 to 30 years. In this study, the average age of the participants was 37.82±6.96 years. Perhar R et al[12] in their study reported "the most common age group affected by Leiomyoma was found to be in the 4th decade between 36-40 years" which is identical to the present study. Results were also identical to research done by Singh P et al[13] who revealed "cases presenting with UF were of 36-45 years of age which accounted for 74.3%. mean age of presentation was 37.89 years.

Ahmed M Mostafa et al[14] reported that mean age of the females of the control group was 34.81 years (range 27-40). The age distribution of UF in study done by Satpathy T et al[15] showed that 37.9% of patients belonged to the 5th decade whereas Sunith et al[16] reported 33.5% and Abdullah et al[17] showed 33.1%. The incidence of abnormal intrauterine bleeding in patients with median age of 41 years has been described in numerous prior investigations.[18,19] It was also noted in the previous study that young women's abnormal uterine bleeding was frequently misdiagnosed as dysfunctional bleeding which could cause a delay in diagnosis.[20]

63% of the subjects in this study were nulliparous. 2nd and 3rd parity wererevealed in 24.5% of the subjects while 4th and above parity was found among 12.5% of the subjects. Similarly, Perhar R et al[12] in their study showed that most of the subjects (91.66%) were second para.

Maximum subjects were having lower SES (44.5%) followed by upper lower SES (31%). Lower middle, upper idle and upper SES was reported in 15%, 6.5% and 3% respectively. According to Perhar R et al[12], more than half (58.3%) patients belonged to lower middle class.

Most common complaint among the study subjects was menorrhagia (62%) followed by dysmenorrhea (38.5%). Infertility, polymennorhoea, pain in abdomen and vaginal discharge was reported among 9%, 8%, 6% and 4.5% respectively. Perhar R et al[12] in their study reported that more than half (88.3%) cases presented with heavy menstrual bleeding at the beginning of the treatment followed by dyspareunia (11.66%) and infertility (6.66%) while only 5% cases

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were asymptomatic.

Family history viz. fibroid, diabetes and cancer wererevealed in 12%, 9.5% and 1.5% of the subjects respectively. Overweight and obesity were reported among 29% and 31.5% of the subjects respectively. Cibiera et al[21] in 2016 found that higher TGF-b3 serum concentration, higher BMI and positive family history increases the probability of developing uterine fibroids. At baseline, mean PBAC score was 153.36 which reduced to 84.91 and 61.03 after 3 and 6 months respectively. When PBAC score was compared statistically at 3 and 6 months with baseline score, significant ($p<0.05$) difference was reported in this study.

Similar to the present study, Saharan S et al[22] found a statistically significant reductions in PBAC score from 111.52 to 2.36. In a study done by Perhar R et al[12], Tripterygium Wilfordii with Vitamin D led to significant decrease of mean PBAC score from 160.20±35.23 to 61.20±37.31. This is similar to the present study.

At baseline, mean VAS was 2.76 which reduced to 1.21 and 0.40 after 3 and 6 months respectively. When VAS was compared statistically at 3 and 6 months with baseline score, significant difference was found at $p<0.05$ in this study.

The mean VAS score at baseline was 2.45±2.03 in Tripterygium Wilfordiiwith Vitamin D group which was significantly reduced to 1.20 at follow-up as described by Perhar R et al[12] in their study. Similar to the present study, Saharan S et al[22] in 2016 found a statistically significant reductions in VAS score 6.24±0.93 at the beginning of treatment to 1.28±0.74.

Before intervention, UF size was approximately 5.90. After 3 months of intervention, size was reduced significantly in subserous and intramural but no significant change was reported in submucous. Similar findings were revealed after 6 months. Before intervention, UF volume was approximately 22.5. After 3 months of intervention, volume was reduced significantly in subserous and intramural but no significant change was reported in submucous. Similar findings were revealed after 6 months. In accordance with the present study, Zhongua et al[23] conducted a study on Tripterygium Wilfordii with vitamin D and found significant reduction of 51.6% in the size of Leimyoma. For vitamin D, Sharan et al[24] reported that it inhibits fibroid cell growth through the suppression of catechol - O-methyltransferase (COMT), an enzyme linked to the pathogenesis of UFs. Halder et al[25] showed that vitamin D consistently reduced TGF-B3 effects that are involved in the process of fibrosis in human Leiomyoma cells. TGF-B3 upregulated the synthesis if many of extracellular matrix proteins like fibronectin and collagen type I expression that are associated with tissue fibrosis.

Al-Hendy et al[26] demonstrated that decreased estrogen induced UF cell proliferation following vitamin D treatment. Indeed, compared to normal myometrium, the expression of ER- α and progesterone receptors (PR-A and PR-B) inversely correlated with vitamin D receptor expression in fibroid tissue. These effects demonstrate that vitamin D antagonizes sex hormones in fibroid cells and therefore may have a role as anti-fibroid treatment. In 2016, Ciavattini et al[27] demonstrated that vitamin D treated women displayed a reduced disease progression in relation to small UF.

Collectively, considering the effectiveness for myomas reduction and its safety profile, vitamin D has emerged as a notable candidate for fibroid treatment and possibly for their prevention.

In the present study, side effects viz. nausea and vomiting, headache, abdominal pain and infrequent menstruation was revealed in 3.5%, 2.5%, 2.5% and 46% of the subjects respectively. Non-hormonal drugs are associated with no major side effect and better compliance of the patients as stated by Perhar R et al[12] in their study.

Limitation of our study is the small number of cases and short-term follow-up. Therefore, further longitudinal studies with large sample size should be conducted. Clinicians managing women with UF should counsel their patients regarding medical management including the non-hormonal treatment before surgical treatment.

CONCLUSION

It was discovered that non-hormonal medications were helpful and efficient in decreasing sign and symptoms (menorrhagia, dysmenorrhea, polymenorrhoea, pain in the abdomen, fibroid size and volume) and thus general condition of the women. Due to lack of research, the available data does not the use of Tripterygium Wilfordii in conjuction with vitamin D, although it did provide a promising effect in terms of a reversibly inhibitory effect on the ovary with negligible reverse effects. It was seen that it was cost-effective. In this study, we have calculated sign and symptoms score and it was seen that good and mild effect was seen in 58% and 34% respectively while no effect in 8%. While this study has demonstrated that non-hormonal treatment significantly reduces the volume of fibroids and reduces symptoms, further investigation is required to determine how long these advantages will last when treatment is stopped.

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