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EFFICACY OF TWO AYURVEDA DRUG REGIMENS FOR UTERINE FIBROIDS, A RANDOMIZED, SINGLE BLIND, THREE-ARM, CLINICAL TRIAL- STUDY PROTOCOL

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ABSTRACT: Uterine fibroids are the most common genital tract tumor in reproductive age women. The main treatment option for fibroid is surgical intervention. Options for medical therapy are currently limited to preoperative reduction of symptoms related to uterine bleeding and fibroid size. Ayurveda treatment for this condition is widely practiced in Sri Lanka. We aimed to evaluate the efficacy of two Ayurveda treatment regimes in patients with uterine fibroids. The study is designed as a randomized, single blind, three arm clinical study with 30 participants in each arm. Participants diagnosed with uterine fibroids size 2 cm or more and meet the inclusion criteria are enrolled to this study. Arm I and Arm II undergo two Ayurveda treatment regimens and Arm III is the control group. Endpoint will be calculated from baseline in volume of the largest fibroid by two dimension ultrasound scan after 12 weeks of treatment intervention and repeat in four weeks follow up. Clinical improvements and quality of life is assessed by Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL). Effect of therapy on each arm is assessed based on the Ayurveda body constitution (Prakriti). Haematological investigations are conducted before and after the treatment as safety parameters. Statistical analysis will be done using SPSS version 16. All statistical tests will be performed, two-tailed with significance determined by reference to the 5% level. Outcome of this study will be to developed evidence-based effective alternative to standard methods of treating uterine fibroids.

INTRODUCTION: Uterine fibroids (leiomyomas or myomas) are the most common benign neoplasm of the uterus [1], is known to occur in 20%-40% of reproductive age females [2]. Abnormal uterine bleeding, pain and complaints related to pelvic pressure are common symptoms associated with this condition [3]. These can have a remarkable impact on women's health.

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To date, most therapy for fibroids has been surgical, either myomectomy or hysterectomy. Surgical interventions require general anesthesia, lengthy hospital stays, and long recovery periods. Therefore, it would be highly desirable for the condition to be treated as conservatively as possible.

In this context, various complementary and alternative medicine treatments have been administered for uterine fibroid, including Sri Lankan Ayurveda, the most popular complementary medicine in Sri Lanka. From the few trials that are available, it is difficult to reach firm conclusions due to the quality and the small sample sizes.

The purpose of this study is to establish basic clinical efficacy and safety data for two Ayurveda drug regimens. All the drugs selected for the study are documented in texts [4, 5, 6]. According to an observational study did kaumadik *et al*., 2016 [7] found that selected drug regimen has been widely used in the treatment of uterine fibroids in the system of Sri Lankan Ayurveda. But these regimes have not been clinically tested for efficacy and safety on uterine fibroids. Therefore we have designed a Randomized Clinical Trials to detect the efficacy and safety of these drug regimens.

METHODOLOGY:

Design of the Study: This study is designed as a randomized, single-blind, three-arm clinical study with 30 participants in each arm.

Recruitment of Cases: Women seeking treatment for uterine fibroids will be screened for inclusion and exclusion criteria for participation in the study. Women with uterine fibroids confirmed by ultrasound scanning, CT, MRI, or a combination of these modalities will be eligible to be included.

The participants will be provided with a detailed information sheet supplemented by a verbal explanation. They will be reviewed at a later date to obtain informed written consent to give them an opportunity to discuss their participation with family and other relevant persons. Consented participants will be recruited to the three arms **Fig. 1**. Demographic data and other basic information will be collected at the same time.

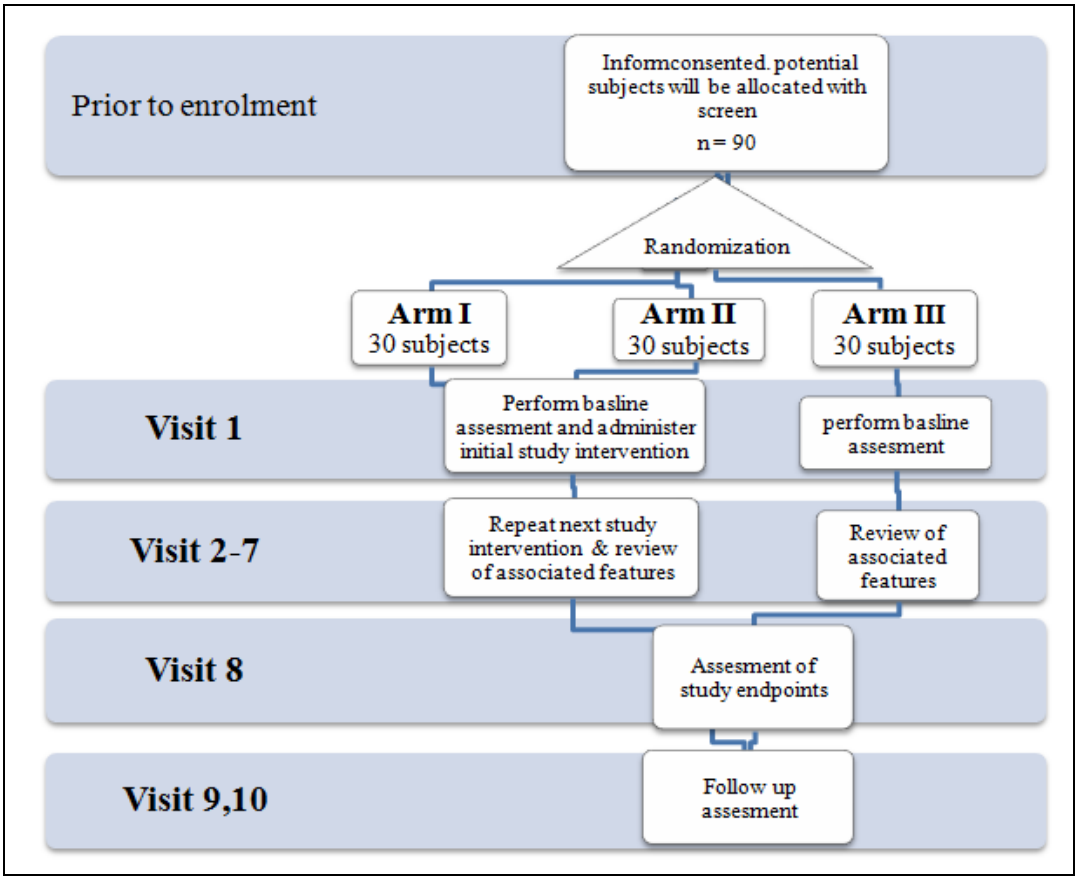

FIG. 1: STUDY FLOW CHART

Participant Inclusion Criteria: Women aged between 18 to 50 years [8] will be included. They need to have the ability to take medication, be willing to adhere to the medication regimen, willing and able to give informed consent to be included in the study. At least one fibroid of diameter ≥2 cm confirmed by pelvic ultrasound must be present [9].

Participant Exclusion Criteria: Women with a history of having had hormonal steroid therapy for a minimum of 03 months prior, pregnancy or desire to become pregnant within the study period, lactating mothers, menopausal women and those who are not within the inclusion age limits will be excluded. Fibroid cases who have heavy menstrual bleeding will also be to prevent interruption of the

treatment protocol. To ensure correct clinical assessment, conditions other than fibroids contributing to dysmenorrhoea or pressure symptoms will be excluded. Presence of any severe medical or psychological condition that, in the opinion of the investigators, would compromise the patient's safe participation will also be excluded. The exclusion will be primarily based on the information provided by the patients. Menorrhagia will be excluded with the help of menstrual assessment chart [10].

Sample Size and Randomization: The Sample size was estimated that would be sufficient to detect significant differences in the quality of life improvement and the change of the size of fibroid by ultrasound scan between the experimental and control group. The sample size was calculated with the main outcome parameter as a reduction in uterine leiomyoma size [11]. For a quantitative outcome,

$\mu 1$ = Anticipated mean response for standard Rx
σ = Anticipated standard deviation of standard Rx
$\mu 2$ = Anticipated mean response for new Rx
α = Level of significance(to detect a treatment difference)
β = Degree of certainty that a difference in (P1-P2) if present would be detected

$$n = 2\,\sigma^2 \times f_{(\alpha,\beta)} \,/\, (\mu_1 - \mu_2)^2$$

$$f = (Z_{\alpha/2} + Z_{\beta})^2$$

Control group $\mu 1 = 0$
Treatment group $\mu 2 = 28\%$ (assumed a $\mu 2 = 10\%$)
SD = 10%
$Z_{\alpha} = 1.96$ for $\alpha = 5\%$
$Z_{\beta} = 1.28$ for $\beta = 90\%$
N = 20
Add loss to follow up = 30

Consecutive consenting sample method will be followed to select participants of the first two arms for the study. A blocked design will be used, using an online statistical computing web programming [12] to generate the randomization schedule, 14 sets of 2 unique numbers per set range from 1 to 2 (representing arm I and arms II) were used. Arm III was selected by non-randomized purposive sampling method.

Treatment Protocol: Participant of Arm I and Arm II will receive a treatment regimen for twelve weeks. Oral administration and external administration will be performed according to the following method **Table 1**. Participants with uterine fibroids that fulfilled the recruitment criteria scheduled for myomectomy or hysterectomy after a minimum of three months from the day of recruitment will be recruited. They will be assessed at fortnightly intervals without drug intervention. All the participants of the treatment groups will be blind to treatments. The method of administration is described in **Table 1**.

TABLE 1: METHOD OF DRUG ADMINISTRATION

	Arm I	Arm II	
Period of a Drug intervention	Panchamoolilaghudrakshadi decoction [5]		2 Weeks
	Pill –Chandraprabhavati [4]		
	Manibadra powder [5]		
	Thiplagugul decoction [13]	Punarnavashtaka decoction [4]	10 Weeks
	Pill- Panchatiktagritaguggul [4]	Pill- Kanchanaragugulu [4]	
	Krishnajeeraka powder [5]	Satakuppa powder [5]	
	Sharshapadi oil [4] - external application	Nirgundyadi oil[4]– external application	
Follow up	04 weeks		

Study Drug Formulations and Dosage:

TABLE 2: STUDY DRUG FORMULATIONS AND DOSAGE

S. no.	Drug	Dose	Mode of administration	Route
1	Panchamoolilaghudrakshadi Decoction	30 ml	bd before meals	Oral
2	ThiphalGugul decoction	30 ml	bd before meals	Oral
3	Punarnavashtaka decoction	30 ml	bd before meals	Oral
4	Chandraprabhavati	2 pills (500mg × 2)	bd after meals	Oral
5	Panchatiktagritagugulu	2 pills (500mg × 2)	bd after meals	Oral
6	Kanchanaragugulu	2 pills (500mg × 2)	bd after meals	Oral
7	Manibadra powder	Powder 05g phanta	At night	Oral

8	Krishnajeeraka powder	Powder 05g phanta	bd after meals	Oral
9	Satakuppa powder	Powder 05g phanta	bd after meals	Oral
10	Sarshapadi oil	05ml apply lower abdomen	07 days after cessation of menstruation	External
11	Nirgundyadi oil	05ml apply lower abdomen	07 days after cessation of menstruation	External

Packaging and Dispensing: Satakuppa powder and Krishnajeeraka powder, single ingredient drugs used for the study are prepared at the Department of Pharmacology and Pharmaceutics, Institute of Indigenous Medicine under standard GMP conditions.

Other drugs are purchased from Sri Lanka Ayurveda Drug Cooperation, Department of Ayurveda, Navinna, Sri Lanka. Liquid drugs (decoctions and oil) are bottled in sterilized glass bottles with sealed plastic lids. Tablets and powders are packed in light and waterproof sealed plastic containers.

Each drug is packed for 14 days and labeled indicating the batch number, arm, dose, time of administration, mode of administration (oral or external use), *etc*. Drugs are stored in the pharmacy and will dispense to the study participants at each visit with instructions, and a therapeutic diary is provided for all.

Treatment compliance will be assured by visual inspection of the drug containers, which will be carried by the patients at every clinic visit and questions by the investigator.

Arm III (control group) will be selected from De Soysa Hospital for Women (Teaching), Colombo 08, Sri Lanka. Participants with uterine fibroids who fulfill the recruitment criteria and scheduled for myomectomy or Hysterectomy on or after 03 months will be recruited. They will be assessed to evaluate associated features at four weekly intervals at the same clinic, but no drug intervention will be performed.

Follow Up: Study participants will be followed up for four weeks after drug administration period ones on a fortnightly basis. Associated features will be assessed in each visit and USS will be performed in the last visit (Visit 10).

Patient Safety: At the first visit a blood sample (5 ml) will be obtained under aseptic conditions into a sterile centrifuge tube *via* venous puncture by an experienced nurse and send immediately to a relevant laboratory for assessing. All patients will undergo routine testing that included FBC, AST/ALT, and serum creatinine/GFR), Estradiol (E_2), FSH Levels, urine full report before (Visit 1) and after the treatment (Visit 8) **Table 3**. Vital signs will be measured at each visit.

TABLE 3: DATA COLLECTION SCHEDULE

Period	Screening	A treatment period (12 Weeks)								Follow up	
Visit		1	2	3	4	5	6	7	8	9	10
Informed consent	Δ										
USS report	Δ								Δ		Δ
Demographic characteristics	Δ										
Safety assessment		Δ							Δ		
UFS-QOL questioners		Δ									
Assessment of Prakriti	Δ										
Hormone assessments		Δ							Δ		
Review of associated features		Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ
Treatment compliance			Δ	Δ	Δ	Δ	Δ	Δ	Δ		
Adverse effects			Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ	Δ

Primary Outcome Measures: USS will be used to determine the primary outcome. Change from baseline in volume of the largest fibroid will be measured. TVS/TAS will be done at the end of 12 weeks (Visit 8) and again after one month at follow up (Visit 10). Clinical improvement of the size of fibroid will be evaluated by comparing with baseline scan with the help of 2D Ultrasound scan. Measurements will be calculated by measuring ovoid volumes by using the longer and shorter diameter with the determination of their mean values [14]. Necessary steps will be taken to blind the ultra-sonographer.

Secondary Outcome Measures: Symptom severity and their impact on (Health-Related Quality of Life) HRQL will be assessed by a Uterine Fibroid Symptom and Health-Related Quality of Life Questionnaire (UFS-QOL) [15] which is already validated in a small population at the same study centers.

Body constituent (Prakriti) is identifying of each at the screening with the help of a questionnaire [16]. Effect of therapy according to the body constituent will be evaluated at the end of the study. Changes in the hormone levels; estrogen (E_2) and FSH will be studied by comparing before and after treatment values.

Statistical Analysis: Statistical analysis will be done using SPSS version 16. All statistical tests will be performed, two-tailed with significance determined by reference to the 5% level.

Data and Safety Monitoring: Monitoring will be conducted for quality control of the trial. Research subjects will be routinely questioned about adverse events at study visits. All observed or volunteered adverse events (serious or non-serious) and abnormal test findings, regardless of a study group or suspected causal relationship to the study drug (s) will be recorded in the subjects' case histories. Data will be reported to ERCIIM without undue delay.

Ethical Consideration: This study protocol was approved by the Institutional Review Board of the Faculty of Graduate study, Colombo University, Sri Lanka. Ethical clearance was obtained from the Ethical Review Committee of Institute of Indigenous Medicine, University of Colombo (ERC No: 17/68).

DISCUSSION: Uterine fibroids are treated with herbal medicine in many traditions and countries [17]. The study conducted by Jian Ping *et al*., [18] says studies on the use of herbal preparations for the treatment of uterine fibroids are limited due to scientific validity as there is a limited number of studies that are of low in quality. The use of herbal medicines for uterine fibroids may not be warranted unless firm evidence of their efficacy and safety has proved. Therefore this type of trial protocol will be helpful to provide evidence-based scientific data on this subject area.

By this trial, it is expected to discover that, the comprehensive treatments of Ayurveda can be more helpful for improved quality of life compared with the control group. Again safety of drug regimens could also measure by the study. Ayurveda describes a unique concept, Prakriti (constitution), which is genetically determined, categorizing the population into several subgroups based on phenotypic characters like appearance, temperament, and habits. The concept is claimed to be useful in predicting an individual's susceptibility to a particular disease, the prognosis of that illness and selection of therapy. Effect of therapy will be analyzed by an individual's constitution. The strengths of the study are its randomized single-blinded design, protocol publication and the recording of patient-reported complications. The limitations of the study could be slow patient recruitment because of the eligibility criteria and a single study setting.

CONCLUSION: Outcome of this study will be to develop evidence based effective alternative to standard methods of treating uterine fibroids and to validate the current practice in Ayurveda for uterine fibroids. This trial could emphasize the importance of individualized treatment for participants with uterine fibroids on basis of body constituent (Prakriti).

Trial Status: Recruitment of participants will commence in May 2018, and final results are expected to be available in April 2019.

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CONFLICT OF INTEREST: The authors declare that they have no conflicts of interest regarding the publication of this manuscript.

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