Journal of Pharmaceutical Research International

Volume 36, Issue 3, Page 1-9, 2024; Article no.JPRI.114066
ISSN: 2456-9119, NLM ID: 101716968
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Randomized, Single Blind, Standard Controlled, Equivalence Clinical Trial to Evaluate the Comparative Efficacy of Eladi Kasaya Versus Tranexamic Acid Tablet in the Management of Asrigdara (Heavy Menstrual Bleeding): A Clinical Trial Protocol

Trapti Agrawal [a*], Saunitra Inamdar [b], Hemanta Kumar Panigrahi [c] and Pratiksha Rathod [a]

[a] Department of Prasutitantra and Striroga, Mahatma Gandhi Ayurvedic College, Hospital and Research Centre (MGACH & RC), Datta Meghe Institute of Medical Sciences, Wardha, Maharashtra, India.
[b] Department of Obstetrics and Gynaecology, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, Maharashtra, India.
[c] Department of Shalya Tantra, Central Ayurveda Research Institute, Punjabi Bagh, New Delhi, India.

Authors' contributions

This work was carried out in collaboration among all authors. Author TA has designed, wrote the protocol, performed statistical analysis and prepare the first draft of manuscript. Authors SI, HKP and PR managed literature search and analysis of the study. All the authors read and approved the manuscript.

Article Information

DOI: 10.9734/JPRI/2024/v36i37502

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/114066

Study Protocol

Received: 03/01/2024
Accepted: 08/03/2024
Published: 13/03/2024

**Corresponding author: E-mail: tripti.obs@gmail.com;*

ABSTRACT

Introduction: Excessive menstrual bleeding is a common problem in reproductive age group females, and it is reported that 1 in 20 lifetime chances, a female needs consulting the physician for excessive and prolonged menstrual bleeding. Ayurvedic literature describes excessive menstrual bleeding as Asrigdara (HMB). Eladi kasaya is one of the treatment modalities for heavy menstrual bleeding given in classics and hence chosen for the current clinical trial.

Methods: We planned a prospective, randomized, controlled, and equivalence trial on the patients with Heavy menstrual bleeding (blood loss > 80 ml) for the last two cycles or more. Eladi Kasaya 50 ml with honey and sharkara(sugar) thrice a day will be given from day 1 to day 7 for 3 consecutive menstrual cycles to Group A and Tablet Tranexamic acid 500mg thrice a day to Group B. Primary outcome measures are menstrual blood loss improvement, reduction in pain assessed by visual analog scale, and change in Haemoglobin concentration. The secondary outcome measure is improvement in quality of life. All adverse drug reactions will be monitored and reported to Ayush Suraksha, pharmacovigilance center, Maharashtra. Following sample size calculation 46 patients will be recruited in each group to demonstrate equivalence with 80% power. The duration of study will be 2 years. The study is approved through Institutional Ethics Committee dated 07/10/2022, MGACHRC/IEC/Oct-2022/585. Participant recruitment shall be started after getting registered with the Clinical Trial Registry of India.

Results: Current manuscript is a clinical protocol, hence results are yet to derive from the study. Results will be presented in conferences and shall be attempted to publish in indexed/peer-reviewed medical journals.

Conclusion: Conclusion shall be drawn after completion of the clinical study.

Keywords: Eladi kasaya; asrigdara; tablet tranxemic acid; heavy menstrual bleeding.

1. INTRODUCTION

The human reproductive system is a complex system and the diseases related to reproductive system seriously affect the physical and psychological health of individual specially women. National Health Portal of Govt. of India reports Heavy Menstrual Bleeding (HMB) occur in 9 to 14% of women between menarche and menopause [1]. Normal menstruation denotes the healthy state of the female reproductive system, but if the menstrual cycle becomes abnormal with excessive and/or prolonged bleeding associated with deranged frequency is indicative of some underlying pathology [2].

Ayurveda classics refers the Heavy menstrual bleeding as *Asrigdara*, characterized as cyclical or acyclical, excessive and prolonged menstrual bleeding with bodyache [3]. It is considered under *pitta avritta apana vayu vikara and rakta pradoshaja vikara* [4,5]. Excessive menstrual bleeding may cause anemia and dysmenorrhea and impacts social, economic and psychological health of a woman [6]. Prolonged and excessive menstrual bleeding without endometrial, uterine and endocrinal pathology have been poorly understood [7]. In conventional medicine, Tranexamic acid (Anti-fibrinolytic drug) is the preferred treatment for the Heavy menstrual bleeding [8], with some noticeable side effects. Hence the study is planned to explore Ayurveda medicine for the treatment of Heavy menstrual bleeding. Fundamental principles of *Ayurveda*, like *Vatahara ckikitsa (pacify vata), Kapha-Pitta Shamaka (pacifier), Deepana-Pachana (digestive), Rakta Shodhaka (blood purifier)* and *Rakta Stambhaka (hemostatic)* are found to be effective in relieving uterine disorder [9]. *Eladi kasaya* is one such combination for the management of Heavy menstrual bleeding. [10] *Eladi kasaya* consist of *Ela (Elettaria cardamomum), Samanga (Mimosa pudica), Shalmali (Salmalia malabarica), Haritaki (Terminalia chebula)* and *Maghdhika (Piper longum)*. It also helps to manage associated symptoms like anemia, pain and weakness. The protocol is designed to study whether *Eladi kasaya* is as efficacious as *Tablet Tranexamic acid* in the management of *Asrigdara* (Heavy menstrual bleeding).

2. METHODS

The protocol is developed to study whether the *Eladi kasaya* is as efficacious as *Tablet Tranexamic acid* in the management of Asrigdara (Heavy menstrual bleeding) among enrolled participants. CONSORT flow chart of clinical study protocol is shown in Fig. 1.

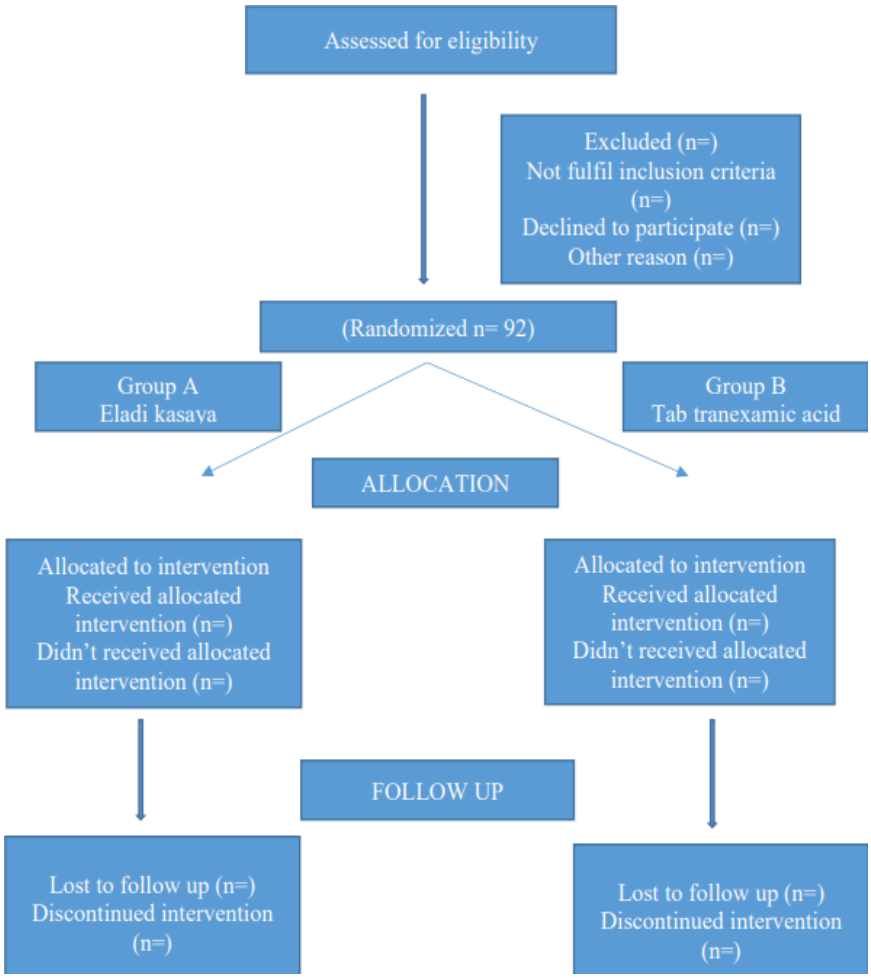

Fig. 1. Consort flow chart of the clinical protocol

This will be a prospective, randomized, single blind, parallel group, standard controlled, single centre study on patients having menstrual blood loss more than 80 ml from two or more cycles with an equivalence design. The trial will be conducted at Mahatma Gandhi Ayurvedic College and Hospital & Research center, Salod(H), Wardha. Eligible search at *Prasuti tantra* and *stri roga* OPD and IPD will be made. Such patients will be contacted personally and will seek consent after describing complete information about study. They will be enrolled and randomized to either of the two study groups (*Eladi kasaya* or Tablet Tranexamic acid). Enrolled subjects will be evaluated for clinical, and laboratory measures as per Clinical research Form (CRF). Ayurveda evaluation will also be done through CRF. Assessment criteria is shown in Table 1, 2.

All the participants will be monitored for amount of blood loss through pictorial blood assessment chart (PBAC), pain through visual analog scale (VAS), haemoglobin level, drug safety, Quality of life (QoL) by menorrhagia impact questionnaire and occurrence of any adverse event. The final data analysis will be carried out after successfully completing the study of said number of patients at end of 2 years.

2.1 Recruitment, Screening, Consent

Patients with heavy menstrual bleeding (>80ml), assessed through PBAC, for at least 2 or more consecutive cycles will be included in the study. Ninety two participants will part in study. An information sheet will be provided to participants detailing complete study protocol, and participant's rights. Head to head discussion for all queries would be invited. Voluntary decision shall not be further persuaded. After full satisfaction, consent form signature shall be obtained. Participants cleared inclusion and written consent will be randomized and enrolled.

Table 1. Assessment schedule of the clinical protocol

Visit	Screening Visit	Visit 1 Enrollment & randomization (day 0)	Visit 2(8th day of 1st cycle of menses)	Visit 3 (8th day of 2nd cycle of menses)	Visit 4 (8th day of 3rd cycle of menses)	Visit 5 (8th day of 4th cycle of menses)
Consent	+					
Initial demographic details	+					
Inclusion exclusion criteria	+					
Medical history	+					
Associated Symptoms	+		+	+	+	+
Randomization		+				
Complete physical examination	+	+	+	+	+	+
Menorrhagia impact questionnaire		+				+
PBAC score	+		+	+	+	+
VAS for lower abdominal pain and low backache	+		+	+	+	+
Adverse event assessment			+	+	+	+
Completion and outcome report						+

VAS-Visual Analog Score, PBAC score- Pictorial Blood Assessment Chart

Table 2. Laboratory investigations Schedule of the clinical protocol

Visit	Screening Visit	Visit 1 Enrollment & randomization (day 1)	Visit 2(8th day of 1st cycle of menses)	Visit 3 (8th day of 2nd cycle of menses)	Visit 4 (8th day of 3rd cycle of menses)	Visit 5 (8th day of 4th cycle of menses)
Complete blood count	+					+
FBS	+					
Bleeding time, clotting time	+					
Liver function test	+					
Renal function test	+					
Ultrasound pelvis	+					+

2.2 Eligibility

2.2.1 Inclusion criteria

Patients with heavy menstrual bleeding (>80ml) assessed through PBAC, for at least 2 or more consecutive cycles with 24-35days interval; Age group of 18 to 45years; Patients willing to comply with study protocol requirements will be registered.

2.2.2 Exclusion criteria

Patients with any diagnosed uterine organic pathology, hypertension, diabetes mellitus, congestive cardiac failure; Coagulopathy; Liver dysfunction; Thyroid dysfunction; malignancy; abortion in last three months; active genital tuberculosis; uterine polyp or erosion; Intrauterine contraceptive device in utero, pelvic endometriosis; Hemoglobin < 8 gm/dl would be the exclusion criteria.

2.2.3 Withdrawal criteria

Any enrolled participant not willing to continue the protocol with or without any reason or if the patient discontinues the trial drug for more than 03 days at a time, she will be withdrawn from the study with proper data recordings to be analyzed at the end of the proposed trial.

2.2.4 Randomization

The participants eligible for enrolment will be randomized in a 1:1 ratio to *Eladi kasaya* group or Tablet Tranexamic acid group, in accordance of a randomization scheme using a computerized system.

2.2.5 Monitoring

Participant will be clinically evaluated on all subsequent visits by clinician / researcher till the completion of the visits. Regular telephonic contact will also be maintained for instruction and reminders once in 2 weeks till the study completes.

2.2.6 Compliance

Participants will be encouraged to remain adhered to treatment protocol and instructions given as per protocol. Medication logs will be maintained for both the groups. Morisky medication adherence scale will be adopted to evaluate medical compliance [11]. Regular telephonic contact will also be maintained for instruction and reminders.

2.2.7 Trial intervention

The study includes two groups *as Eladi Kasaya* and *Tablet Tranexamic acid*. The Tranexamic acid is the preferred treatment for heavy menstrual bleeding. Thus, Tablet Tranexamic acid group will serve as a control to ascertain the equivalent effects offered by *Eladi kasaya*. Posology and other instruction for both the group is given Table 3.

2.2.8 Formulation preparation, distribution, and follow-up

Eladi kasaya ingredients and their used part are shown in Table 4 and Fig. 2 [12-28]. All herbs will be phenotypically validated by taxonomist/ *Dravyaguna* expert. Further HPTLC fingerprinting will also be done for *Eladi Kasaya. Eladi kasaya* will be prepared and packed at institute pharmacy. It will be stored at an optimum temperature till further use. All instruction regarding Kasaya preparation and uses will be demonstrated with a video to participants and the video will also be sent to them with the help of social media. Drug shall be distributed through Patient Department of institute by researcher. Follow-up shall be done as per table 1 for physical and clinical signs evaluation till completion of study protocol.

Table 3. Posology of the clinical protocol

Groups	A	B
Intervention	*Eladi kasaya*	Tablet Tranxemic acid
Form, Dose & frequency	*Kasaya*, 50ml, thrice a day	Tablet,500mg, thrice a day
Anupana	Honey and sugar	Water
Duration	From day 1 of menses to day 7 for 3 consecutive cycle	From day 1 of menses to day 7 for 3 consecutive cycle
Follow ups	8^{th} day of each 3 consecutive cycle and 8^{th} day of 4^{th} cycle without intervention	8^{th} day of each 3 consecutive cycle and 8^{th} day of 4^{th} cycle without intervention

Table 4. Part used and pharmacological properties of ingredients of Eladi *Kasaya*

Name of drug	Ela	Samanga	Shalmali	Haritaki	Maghdhika
Latin name	Elettaria cardamomum	Mimosa pudica	Salmalia malabarica	Terminalia chebula	Piper longum
Family	Scitamineae	Mimosoidae	Bombacaceae	Combretaceae	Piperaceae
Rasa (Taste)	Katu, madhura	Kashaya, Tikta	Kashaya	Panch rasa alavana	Katu
Guna (Property)	Laghu, ruksha	Laghu, Ruksha	Laghu, Snigdha, Pichhila	Laghu, ruksha	Laghu, snigdha, tikshna
Virya (Potency)	Sheeta	Sheeta	Sheeta	Usna	Anusna sheeta
Vipaka (Metabolism)	Katu	Katu	Katu	Madhura	Madhura
Karma (Action)	Vatahara	Sandhaniya	Stambhana	Prajasthapana, adhobhagahar	Yogavahi
Used part	Phala (fruit)	Moola (root)	Niryasa (exudate)	Phala (fruit)	Phala (fruit)
Chemical constituent	Sitosterol, farnesol	Mimosine, turgoin	Tannic acid, Gallic acid	Chebulic acid, gallic acid, ellagic acid	Piperine

Fig. 2. Part used and pharmacological properties of ingredients of *Eladi Kasaya*

2.3 Clinical Outcomes

2.3.1 Primary outcome measures

Primary outcome will be measured through reduction of blood loss calculated by Pictorial Blood Assessment Chart [29] and reduction of pain by Visual Analog Scale and improvement in hemoglobin level.

2.3.2 Secondary outcome measures

Researcher will evaluate safety of given medication/instructions through occurrence of adverse drug reaction and QoL assessment using Menorrhagia impact questionnaire [30].

2.3.3 Adverse events

All adverse events during the study will be recorded, monitored as per ICH-GCP (2016), managed at site or referred as per referral protocol, and reported to the nearest AYUSH Pharmacovigilance Centre. All withdrawal cases will also be evaluated for safety. Severe ADR will be reported to IEC within 48 hours of cognizance. ADR rescue will be done on case to case basis and will be reported to IEC. Participants will be permitted to take rescue medication as and when required for seasonal illness or other health issues, the same will be recorded in the CRF.

2.4 Statistical Analysis

2.4.1 Sample size, power and analysis

The sample size is calculated based on the objective to study whether *Eladi kasaya* is equally efficacious as tablet *tranexamic acid* in the management of HMB. As it is a standard control, equivalence clinical trial to confirm that these two interventions are indistinguishable from each other. The sample size was calculated with 80% power. The calculated sample size for the study is 46 per arms by using formula "N= 2 x (Z1-α/2 +Z1-β / δO) 2 x p x (1 – p)". Data will be analyzed statistically by appropriate inferential statistics using SPSS. Data on discrete will be analyzed using non-parametric tests and data on continuous variables will analyzed using parametric tests. The result will be drawn as n% on discrete variables and mean ± SD on continuous variables. The statistical level of significance will be set at 0.05.

2.4.2 Record retention

All data related to current study will be retained electronically and physically by scholar for at least 5 years from the completion of study or as per Dutta Meghe Institute of Medical Sciences (DMIMS) policy. Data disposal shall also be made as per CTRI guidelines or DMIMS guidelines.

3. DISCUSSION

HMB is a major health care problem, and the only conventionally available treatment is tranexamic acid. It hinders the routine activities of females of reproductive age group and hampers QoL. Such cases are also not uncommon in routine *Stri Roga* Outpatient department. *Ayurveda* advocates a specific principal and herbs to be adopted for *Asrigdara* management. Hence a study is planned to compare the efficacy of *Eladi kasaya*, with Tranxemic acid as the first-choice treatment for excessive and prolonged menstrual bleeding. *Eladi kasaya* has the properties of *deepana-pachana(digestive), vatanulomana (carminative), kapha-pitta shamaka(pacifier), rakta stambhaka (hemostatic) and rakta vardhaka(heamatinic)* suitable for *Asrigdara* management. Considering the concerns about thromboembolic events in patients undergoing anti-fibrinolytic therapy, the *Eladi kasaya* could be a new safe alternative for Heavy menstrual bleeding patients. The final discussion of the study will be written on the basis of results found.

3.1 Strengths and limitations of this Study

Novel Randomized standard-controlled study of *Eladi kasaya* will provide the results status and comparative result. If *Eladi kasaya* shows reduction in blood loss in heavy menstrual bleeding similar to standard drug, it will give the best parallel modality for the management of heavy uterine bleeding. Anti-haemolytic markers assessment has not been done in current study. A fix drug and *anupana* (vehicle) has prescribed irrespective of seasonal, geographical and individual *prakriti* variation.

4. CONCLUSION

Conclusion will be drawn on the basis of statistical analysis of observations of objective and subjective parameters.

CONSENT

As per international standards or university standards, Participants' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

Ethical approval was obtained through the institutional ethics committee of Mahatma Gandhi Ayurvedic College Hospital and Research Centre, DMIMS, Wardha, as per the reference number MGACHRC/IEC/Oct-2022/585, Dated 07/10/2022.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/114066