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CLINICAL STUDY TO EVALUATE THE EFFICACY OF ORAL ADMINISTRATION OF *PRAVAL BHASMA*, *LAKSHADI GUGGULU* AND LOCAL APPLICATION OF *DASHANG LEPA* WITH *PINDA TAIL* ON KNEE JOINTS HAVING ARTHRITIC CHANGES IN HEMOPHILIA PATIENTS

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ABSTRACT

Introduction

Hemophilia is the most prevalent severe genetic hemorrhagic disease. Hemophilia A and B both are attributed to insufficiencies or malfunctions of the corresponding factor VIII and factor IX proteins. The conditions are distinguished by protracted and copious hemorrhage, subsequent to minor trauma or occasionally manifesting independently. Hemophilia C is an additional rare disorder caused by an insufficiency of coagulation factor XI. The most prevalent clinical presentation of severe hemophilia is hemarthrosis. In the absence of proper management, even subclinical hemarthrosis has the potential to progress to hemophilic arthropathy, an incapacitating condition marked by joint degeneration, persistent discomfort and a diminished standard of living; ultimately, surgical treatments becomes necessary. Out of all joints, knee joints are most commonly affected joint in the hemophilia patients as it bears the weight of the body. Presence of advancements in the modern system of medicine, chronic arthropathy continues to be a substantial

concern. Ayurveda has a good command over this symptoms which resemble's to *vatarakta*, hence play a vital role in hemophilic arthropathy.

Methods:

We devised a prospective, open-label, single-arm clinical trial involving participants who volunteered to be screened as part of the project. Constant monitoring with respect to adverse circumstances maintained for the duration of the study. Participants will be monitored on the first, thirty and forty-fifth day. The duration of the intervention is 30 days, an additional 15 days are allocated for follow-up. Inclusion Criteria is: Age between 12 – 40 years & Stage -2/3/4 arthritic changes present in the knee joint. & The patient suffering from moderate to severe Hemophilia (A or B) from factor assay (8 or 9) or having valid registered id card from Hemophilia society or any government hospital showing factor percentage. Source of patients will be from CARI punjabi bagh, LNJP Hospital Delhi and from hemophilia societies.

Result & Conclusion:

As the research remains ongoing, the definitive outcomes and conclusions have not yet been ascertained. IEC has been approved on 11.12.2023 and CTRI/2024/01/061535 [Registered on: 16/01/2024].

Keywords: Hemophilia, Hemarthrosis, Hemophilic arthropathy, *Dashang Lepa, Pinda tail, Praval bhasma, Lakshadi guggulu*

INTRODUCTION

The most prevalent severe hereditary hemorrhagic disorder. Hemophilia A and B are caused by a deficiency or dysfunction of the factor VIII and factor IX proteins, respectively. These conditions manifest as excessive and protracted bleeding following minor trauma or in some cases, spontaneously. Hemophilia C, which is uncommon, is also caused by a deficiency of coagulation factor XI. Occasional manifestations of acquired hemophilia associated with childbirth or age typically resolve with treatment. Hemophilia has frequently been referred to as "Royal's Disease" a term frequently applied to the lineage of Queen Victoria of Great Britain. The earliest ancient historical account pertains to a woman who experienced the loss of her initial two sons as a result of circumcision, as documented in the Babylonian Talmud during the second century AD. The initial account in contemporary history was recorded by Dr. John Conrad Otto, an American physician. A hereditary bleeding disorder was delineated by Dr. Conrad, which was observed to affect

exclusively male offspring of unaffected mothers across multiple families. He later referred to them as "bleeders." The term "hemophilia" was initially recorded in Johann Lukas Schoenlein's dissertation at the University of Zurich, Switzerland. The initial publication of the genetic characterization of hemophilia, Nasse's Law, attributed to Dr. Nasse, established that the condition is exclusively transmitted from unaffected females to their sons **[1-5]**. Hemarthrosis, which refers to recurrent joint hemorrhage, is the most commonly observed clinical presentation of severe hemophilia. In the absence of proper management, even subclinical hemarthrosis has the potential to progress to hemophilic arthropathy, an incapacitating condition marked by joint degeneration, persistent discomfort, and a diminished standard of living; ultimately, surgical treatments become a necessity. Out of all joints, knee joints are most commonly affected joints in the hemophilia patients as it bears the weight of the body. Hemorrhage prevention is critical for the preservation of joint health, given the absence of targeted therapies to mitigate blood-induced synovitis. Chronic arthropathy continues to be a sizable concern notwithstanding the advancements in the modern systems of medicine. In Ayurveda the symptoms of hemophilia resemble *raktapitta* and symptoms of hemophilic arthropathy resemble *vatarakta,* in which there is vitiation of *vata* and *rakta* in *sandhi's*. Ayurveda has a good command over *vatarakta; Ayurveda* can play a vital role in hemophilic arthropathy, which benefits patient in delaying the surgical procedures and improving joint functions along with less pain, leading to an improved quality of life in hemophilia patients.

METHODS AND ANALYSIS

Patient and Public Involvement

The purpose of this protocol is to examine the impact on knee joint pain in the treatment of hemophilic arthropathy. Additionally, it evaluates the clinical efficacy of utilizing *Praval bhasma, Lakshadi guggulu*, and *Dashang Lepa* with *pinda tail* when administered orally and locally in accordance with the protocol. The study's findings will be made public subsequent to their publication in a peer-reviewed journal.

Clinical Trial Registration no: CTRI/2024/01/061535

STUDY DESIGN

This is an open-label, prospective, single-arm clinical trial involving volunteers who are selected for screening as part of the project. At New Delhi's Central Ayurveda Research Institute, the investigation will be carried out. Consenting and qualified volunteers will be

enrolled. An Ayurvedic physician will assess the participants for various clinical and radiological parameters. Additionally, a clinical assessment grounded in Ayurveda will be conducted. The diverse evaluations that are to be conducted are detailed in **Table 1**. Throughout the trial, participants will visit the investigation site three times. The first visit is designated as the screening phase (visit 0). Subsequently, visits 1 and 2 occur after preliminary investigations or baseline, i.e. 1st day, 30th day, and 45th day respectively (visit 3). The investigator shall provide the participants with a thorough explanation of the study and obtain their informed consent during visit 0 (Screening). At the initial visit (baseline), a comprehensive medical history will be gathered. This will include demographic information, pertinent past and present medical conditions or surgical procedures, and concurrent medication data for each participant. The physical examination shall consist of vital sign measurements, including but not limited to height, weight, heart rate, and blood pressure. In subsequent visits, all evaluation instruments will be re-administered and compared to the baseline in order to determine the efficacy of the interventions. Radiological analyses will be conducted in accordance with the case recording file (CRF) at visit one, at the conclusion of active treatment (visit two) and following follow-up (visit three) to assess the effects of Ayurvedic medications on various parameters. A preliminary assessment is scheduled to be conducted after the withdrawal of 60 participants and the conclusion of their 45-day trial period. The ultimate data analysis will be conducted once all participants have completed the study.

Male volunteers between the ages of 12 and 40 were screened for necessary investigations according to the study protocol.

There will be 60 participants in the study. In accordance with national ethical standards, prior to screening, signed informed consent from every participant shall be the responsibility of the investigator. The participant will be given an information sheet detailing the study in a language that is easily comprehensible to them. This sheet will be subject to their review and, if necessary, discussion with the investigator can be done. The participant shall be afforded an adequate amount of time to exercise their voluntary consent to participate. Participants will be encouraged to seek clarification on any uncertainties through the investigator during an in-person interview by asking questions. Upon complete agreement with all aspects of the research study, the participant will be requested to affix their signature to the

consent form. The study physicians will conduct a thorough screening of participants to determine their eligibility and to rule out any contraindications that may prevent them from participating. Those who meet the eligibility requirements will be enrolled. Participants will be monitored at predetermined times as per protocol endpoints, including the baseline, 30th and 45th day.

ELIGIBILITY

INCLUSION CRITERIA

Age between 12 – 40 years

Stage -2/3/4 arthritic changes present in knee joint.

Pre diagnosed patient suffering from moderate to severe Hemophilia (A or B) from factor assay (8 or 9) or having valid registered id card from Hemophilia society or any government hospital showing factor percentage.

EXCLUSION CRITERIA

Age below 12 years and above 40 years

Patient having Mild Hemophilia

Hemophilic patients whose Knee joints are not affected

Having stage 1 arthritic changes

Undergone knee replacement surgery

WITHDRAWAL CRITERIA

Patient not willing to continue

Subject has any life-threatening emergency or severe adverse effects

If subject gets any acute illnesses during the trial, which could affect the study

Left against medical advice.

MONITORING

After the inclusion of participants at baseline, study physicians will conduct physical examinations of participants at each visit. Throughout all time intervals, participant evaluations will encompass comprehensive inquiries into any potential physical symptoms. In subsequent visits, all evaluation instruments will be re-administered and compared to the baseline to determine the efficacy of the interventions. In accordance with the case recording file (CRF) at baseline and at the conclusion of active treatment (visit 3), radiological analyses will be performed to determine the effect of Ayurvedic medications on a variety of radiological parameters. The information is detailed in **Table 1**.

Table 1: Plan of study

	DAY 01	DAY 30	DAY 45
X-RAY (AFFECTED JOINT)	√	√	
USG (AFFECTED JOINT)	√	√	
V.A.S SCORE	√	√	√
R.O.M (AFFECTED JOINT) BY GONIOMETER	√	√	√
QUALITY OF LIFE ASSESMENT	√	√	√
CLINICAL ASSESMENT	√	√	√

COMPLIANCE

Observations will be conducted on the participants to detect any bodily changes, additional symptoms, and adverse effects that may be present. There will be follow-up on the 45th day of the study. Participants who achieve compliance rates of 80% or higher will be permitted to continue with the trial. At 30th day visit, compliance will be evaluated by calculating the approximate amount of medication consumed by each participant. Participants will be requested to return the empty medication container during follow-up appointment. Medication records will be maintained for all prescribed drugs. During each succeeding visit, the participant will be instructed to bring any unused medication for a dosage count to be recorded in the medication journal.

TRIAL INTERVENTION

EXTERNAL MEDICATION

15 -30 gm of *Dashang lepa* mixed with luke warm *pinda tail* and gently apply locally with 4-5mm thickened layer on affected knee joint once a day for 2 hours for 30 days.

INTERNAL MEDICATION-

- *Praval bhasma* – 200 mg capsule once a day with Luke warm milk on empty stomach orally for 30 days.
- *Lakshadi guggulu* – 500 mg thrice a day with Luke warm water after meal orally for 30 days.

CLINICAL OUTCOMES

Primary Outcome

- Improvement in pain by V.A.S score of Hemophilia patients having arthritic changes in knee joint. Time frame [Baseline, 30th and 45th day]

Secondary outcome

- Improvement in Range of Motion ≥15 degree in affected knee joint by goniometer. Time frame [Baseline ,30th and 45th day]
- Reduction in thickness of synovitis ≥1mm in affected knee joint by USG. Time frame [Baseline and 30th day]
- Mild changes in x-ray of affected knee joint. Time frame [Baseline and 30th day]
- Improvement in quality of life in Hemophilia patients. Time frame [Baseline, 30th and 45th day]

CONCOMITANT MEDICATION

Generally, the simultaneous administration of any medication will be limited to an absolute minimum and will always require the consent of a primary care physician and the provision of comprehensive information to the study physician. The concomitant medications will be recorded on the case record form (CRF) by

the study physician. Participants enrolled in the study will receive explicit guidance not to self-administer any additional medication for any condition. Furthermore, they will be required to consult the treating investigator regarding any symptoms, complaints, or unusual sensations. The investigator shall document any pharmaceutical interventions implemented to mitigate the subjects' symptoms. The investigator may authorize the use of any medication necessary to alleviate an emergency. Nonetheless, the same information must be recorded in the corresponding column of the case report form.

STATISTICAL ANALYSIS

Sample Size - 60 (As this is an exploratory study with limited research on hemophilic arthropathy in Ayurveda, hence a sample size has been chosen to be completed in a stipulated time)

Analysis

Means and standard deviations are typical descriptive statistics utilized to summarize continuous variables. In order to summarize categorical variables, frequencies and percentages will be utilized. As required, confidence intervals of 95% will be furnished for descriptive statistics. Prior to conducting inferential analyses on continuous variables, normality tests will be performed on those variables. A transformation will be applied to data that deviates from normal distribution before inferential comparisons are conducted. When transformation of variables is not possible, nonparametric techniques will be applied.

Categorical response models or logistic regression will be utilized to analyze categorical variables. As a threshold for statistical significance, an overall alpha-level of 0.05 will be applied. In conclusion, the missing data in each group will be imputed using the intention-to-treat analysis.

TRIAL CARE AND RECORD RETENTION

The investigator shall maintain all clinical study documents for a minimum of five years following the conclusion of the study, pending further instructions from the CCRAS regarding the proper disposal. Prior to implementation, all protocol amendments will undergo approval by the appropriate Ethics Committees. The investigator is required to promptly inform the appropriate Ethics Committee, study coordinator, and CCRAS within twenty-four hours of any emergency development, whether medical or not, in connection with the clinical study.

DISCUSSION

Hemophilic arthropathy is characterized by progressive joint disease and recurrent hemarthroses, hemophilic arthropathy is a

form of systemic arthropathy that is frequently brought on by hemophilia patient's. Joint dysfunction, persistent discomfort and a diminished quality of life are hallmarks of this incapacitating condition **[6, 7]**.

In Ayurveda, signs and symptoms of bleeding disorders resemble *raktapitta* and hemophilic arthropathy are the damage in joints associated with synovitis caused by repeated bleeding. Signs and symptoms resemble to *vatarakta* in Ayurveda where the sandhi's are affected due to vitiated *vata* and vitiated *rakta* .Here we are administering *Lakshadi guggulu* and *Praval bhasma* out of which *Lakshadi guggulu* has been mentioned for *bhagna, mukta, asthi ruja* in *Bhaisajya Ratnavali, bhagnarogadhikar* 49/13-14 and *Praval Bhasma* has been mentioned for therapeutic use in *sotha* (Inflammation), *Asthi shosh* (Osteoporosis) in The Ayurvedic Pharmacopoeia of India, Part – 1, Second edition, page -613 and as it is also of *sheeta veerya* hence,it will helps in calming down the vitiated *pitta* in *raktapitta*. As synovitis, i.e. inflammation in the synovial membrane of the joint, is also one of the most common cause of pain and stiffness in the joint, local application of *Dashang lepa* with *pinda tail* has been chosen, where *pinda tail* is the *rogadhikar* for *vatarakta* in *charak Samhita Chikitsa Sthan* 29/123 and *Dashang lepa* is mentioned for *sotha* in *bhaisajya ratnavali visarpa rogadhikar 16*.

ETHICS STATEMENT

The IEC CARI New Delhi granted ethical approval. In January of 2024, participant recruitment commenced. Participants agreed to take part in this study with written informed consent.

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CONTRIBUTION OF AUTHORS

Each author either assisted in composing or reviewed and endorsed the final version.

DECLARATION OF CONFLICTS OF INTERESTS:

All authors have provided their consent, affirming that they do not have any research, authorship, or publication of this article.

FUNDING

This study was funded by CCRAS.

Ethics and Dissemination:

The investigation was carried out in adherence to the ethical principles and Indian Good Clinical Practice (GCP) standards, which were derived from the Declaration of Helsinki

for biomedical research and the ICMR ethical guidelines for human subjects (2006). Institutional Ethical Committee granted approval for ethical matters. In May 2024, the recruitment of participants commenced.

Results will be disseminated via preprints and subsequently published in medical journals that undergo peer review.

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