Efficacy and safety of Murivenna anal infiltration compared to Diltiazem topical application in chronic anal fissure: Study protocol for a prospective randomized open-label clinical trial

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Abstract

Background: Anal fissure is a common proctologic condition that causes significant pain and anguish to the patient, significantly impacting the quality of life and wellbeing. There is various treatment options for anal fissures, ranging from pharmacological agents that reduce anal sphincter tone to surgical interventions for cases resistant to medical management. Ayurveda treatments have shown potential for the therapeutic management of anal fissures. This clinical study is aimed to analyse the efficacy and safety of Murivenna anal infiltration compared to Diltiazem topical application in chronic anal fissure.
Methods/design: This is an open-labeled randomized, controlled parallel group clinical trial with a sample size of 66 participants to be randomized and allocated in a 1:1 ratio to two groups. The intervention group will be treated with Murivenna anal infiltration, and the control group will be treated with Diltiazem topical application for period of four weeks. The primary outcome is the proportion of participants who underwent complete healing after four weeks of treatment. The secondary outcome measures will be the proportion of participants demonstrating complete healing after 7 days and 14 days of treatment, respectively, change in pain at or after defecation, cessation of bleeding, and incidence of any recurrence during the study period. Incidence of any adverse events will also be recorded during the trial period.
Discussion: High recurrence rates, adverse effects, incomplete healing, and the negative impact on patient's daily activities and quality of life underscore the need for alternative therapeutic options. Ayurveda offers potential for more sustainable relief with fewer adverse effects. Murivenna oil is time-tested medicated oil effectively used by Ayurvedic physicians for various ulcers of traumatic and pathological origin. This study may provide scientific evidence on the efficacy and safety of Murivenna anal infiltration for chronic anal fissure.
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Abstract:

Background: Anal fissure is a common proctologic condition that causes significant pain and anguish to the patient, significantly impacting the quality of life and wellbeing. There is various treatment options for anal fissures, ranging from pharmacological agents that reduce anal sphincter tone to surgical interventions for cases resistant to medical management. Ayurveda treatments have shown potential for the therapeutic management of anal fissures. This clinical study is aimed to analyse the efficacy and safety of *Murivenna* anal infiltration compared to Diltiazem topical application in chronic anal fissure.

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Introduction:

Anal fissure is a common proctologic condition characterized by intense, prolonged anal pain after defecation, bleeding, and a significant deterioration in the patient's quality of life. Anal fissure, through their symptoms, causes considerable morbidity to the patient. The condition presents with symptoms like severe pain on defecation, which last from a few minutes to several hours, bleeding per rectum, anal discharge, and swelling. If acute, there may be severe pain, and intensity will be comparatively less in the chronic phase. Spontaneous healing of anal fissures is rare due to the reactive spastic contraction of the internal anal sphincter, which diminishes blood flow to the affected area. This constriction impedes the natural healing process, prolonging the duration of symptoms such as pain and bleeding. Therapeutic intervention is often required to alleviate discomfort and promote healing. Various treatment modalities aim to relax the anal sphincter, increase blood flow, and facilitate tissue repair, thereby addressing the underlying cause and promoting resolution of the fissure. Conservative management include bulk agents, stool softeners, warm sitz bath, botulinum toxic injections or topical applications of ointments like diltiazem, glyceryl nitrate etc. [1] Considerable drawbacks are reported, like toxicity, headaches, giddiness, etc, while using these external ointments. Surgical treatment is opted when there is recurrence or failure of conservative management. Surgical treatments include Lord's dilatation, sphincterotomy, and fissurectomy. Complications of surgical treatments include incontinence to flatus and fecus, non-healing external wound, abscess, and fistula formation. [2] Therefore pharmacological modalities for treatment of fissures are opted. The *Ayurvedic* text *Susrutha Samhitha* has mentioned anal fissures as iatrogenic, and has mentioned a condition called *Parikartika* (cutting pain in the anus) in the context of *Vaidya nimitha Bastivyapat* (indiscretion of the clinician while administering medicated enema) and *Gudakshata* (ulceration/injury in the anus) in *Bastinetravyapat* (complications due to the enema pipe). He further says that this condition should be treated in the same way as for the treatment of traumatic wounds. [3] *Murivenna* oil is a time-tested medicated oil used to treat various exogenous and endogenous ulcers. The drugs used for the preparation of oil possess analgesics and anti-inflammatory properties, which reduce pain and spasms and further help in wound healing. Further, the anal infiltration process enables the medicine to be retained in the anal canal for an extended period which can help in reducing the increased sphincter tone and associated symptoms. Hence, this clinical study will compare the effect of *Murivenna* anal infiltration against Diltiazem topical application in the treatment of chronic anal fissures.

Objectives:

The primary objective of the study is to determine the efficacy of *Murivenna* anal infiltration on healing of anal fissure in comparison with 2 % Diltiazem topical application. The secondary objectives are to determine the safety and efficacy of *Murivenna* anal infiltration on reduction of pain & bleeding, and prevention of recurrence of anal fissure in comparison with 2 % Diltiazem topical application.

Materials and Methods:

Study design and setting:

The study is an open label randomized controlled parallel group clinical trial conducted at National Ayurveda Research Institute for Panchakarma (NARIP), Cheruthuruthy, Thrissur District, Kerala, India.

Study participants:

Inclusion Criteria:

Participants of either sex between the age group of 16 - 65 years with a chronic anal fissure persisting for more than six weeks of duration and who are capable of and freely willing to provide written informed consent prior to participation in the study and comply with the study protocol requirements.

Exclusion Criteria:

Individuals with co-morbidities like uncontrolled Diabetes mellitus & hypertension, anemia, malnourishment caused by systemic diseases, fistula in ano, haemorrhoids, perianal abscess, clinically evident fecal incontinence & anal stenosis/fibrosis, inflammatory bowel disease, tuberculous ulcer, malignancies, human immunodeficiency virus, clinically significant renal disease, hepatic disease and cardiovascular disease, psychological diseases (anxiety, depression etc.), active substance abuse and participants on medications hampering wound healing will be excluded. Fissure associated with abscess, drug induced fissures or fissure resulting from external trauma, fissure located at lateral locations and multiple fissures will be excluded. Participants using oral calcium

channel blockers or having sensitivity to intervention drug or calcium channel blockers and those with frequent h/o headaches or on any steroids, NSAIDs, etc., either for fissure or any unrelated disease condition will be excluded from the study. Pregnant and lactating women; and participants who have been using either of the trial interventions within 30 days prior to randomization of the trial will be excluded from the trial.

Study intervention:

Participants in the intervention group will be treated with anal infiltration of *Murivenna* oil for four weeks. On the first week, patient will receive anal infiltration of 30 ml of *Murivenna* oil once daily and for remaining three weeks they will receive anal infiltration of 20 ml of *Murivenna* oil once daily. During the trial period, the participants of intervention group will receive *Triphala choornam* 10 gms at bed time as a mild laxative and the participants will be further advised to do sitz bath with *Triphala kashayam* once in a day. Participants in the control group will be treated with Diltiazem gel 2% for four weeks. Participants will be instructed to apply the gel at least 1.5 cm to 2 cm into the anus on morning and night after sitz bath. During the trial period the participants of control group will receive Lactulose syrup 15 ml bed time as a laxative. Participants in both groups will be advised to consume foods rich in dietary fibre and avoid activities which will cause micro trauma to anus such as prolong sitting, travelling in two-wheelers etc.

Murivenna oil was manufactured at the GMP certified pharmacy of NARIP and *Triphala choornam* was manufactured by GMP certified pharmacy of Central Ayurveda Research Institute, Jhansi, as per the respective standards available in the Ayurvedic Pharmacopoeia of India. [4]

Outcome measures:

The primary outcome is the proportion of participants who underwent complete healing after 4 weeks of treatment. The secondary outcome measures will be proportion of participants having complete healing after 7days and 14 days of treatment respectively, change in pain during or after defecation, cessation of bleeding, and incidence of any recurrence during study period.

Healing of fissure in the present context is defined as disappearance of symptoms and evidence of fissure reepithelization that will be recorded based on the clinical examination and recorded as none, partial, or complete healing at each of the follow-up visits. Mean change in pain intensity during defecation will be recorded in 100 mm VAS scale at each follow-up. Time to an improvement in pain

intensity and proportion of participants who required analgesics for pain relief will also be recorded. Time to achieve cessation of bleeding will also be recorded.

The schedule of enrolment, intervention, assessments, and follow-up visits for the study participants is given in Table 1.

Table 1: Content of data capture

Time of Visit / **Content**	**Screening**	**Baseline 1st day**	**8th day**	**15th day**	**22nd day**	**End of treatment 30th day**	**Follow-up 60th day**	**Follow-up 90th day**	**Telephonic follow-up (each month for 3 months)**		
									1st	**2nd**	**3rd**
Information and Informed consent	■										
Eligibility evaluation	■										
Medical history and Demographic profile		■									
Clinical examination		■	■	■	■	■	■	■			
Assessment of Subjective parameters		■	■	■	■	■	■	■	■	■	■
Laboratory test	■					■					
Drug compliance assessment			■	■	■	■					
Rescue medication assessment			■	■	■	■	■	■	■	■	■
Adverse events assessment			■	■	■	■					
Recurrence of disease							■	■	■	■	■

Safety outcomes:

Participant reported adverse events [AE(s)] during the trial period will be recorded on every scheduled follow-up visit in the structured format. All AE(s) during the study will be monitored and appropriate care would be provided.

Withdrawal criteria:

Participants not willing to continue or non-compliant with the study procedure (Minimum 80% compliance is essential to continue in the study) will be withdrawn from the study. Participants developing life threatening complication or any other severe illness because of other pathology which requires urgent treatment will also be withdrawn from the study. Participants developing serious adverse events (SAE) or treatment induced AE(s) requiring hospitalization will be withdrawn from the study. It will be ensured that such cases will receive appropriate incidental care or will be referred to a higher medical facility if required. The reasons for the withdrawal will be recorded in the participant's case record form (CRF). The same will be informed to the Sponsor and the Ethics Committee within two working days, along with proper justification.

Sample size:

The sample size was calculated based on difference in proportion of participants having complete healing of anal fissure between the study groups. As per previous published study, 25% of participants had complete healing of anal fissure by 4th week of treatment with diltiazem 2% gel and based on the results of a previously published observational study it was assumed that fissure will heal in nearly 60% of participants treated with trial intervention. [5, 6] A sample size of 30 per group is needed to achieve 80% power with 95% confidence interval. Adding an attrition rate of 10%, the sample size per group will be 33. Therefore, a total of 66 participants will be enrolled in the trial.

Recruitment:

Participants from the OPD of NARIP diagnosed with chronic fissure in ano will be screened for the eligibility to participate in the clinical trial. Informed consent will be obtained from the participants before screening. Participants eligible as per inclusion and exclusion criteria will be allocated in either of the study groups based on the randomization schedule.

Randomization & Allocation concealment:

The eligible participants with chronic fissure in ano will be randomized into two parallel groups in the ratio of 1:1 as per a statistician-generated random number sequence using the SPSS software version 15.0. The assignments will be enclosed in sequentially numbered, opaque and sealed envelopes which will be opened by the participants at the time of enrollment.

Compliance:

Compliance with the prescribed medicines will be monitored through a compliance assessment form issued to the participant on each visit. The participants will be instructed to complete the assessment form after each medicine intake and administration. In addition, the compliance will be evaluated by counting the number of containers/tubes returned and the approximate quantity of medications used by the participant. A minimum of 80% compliance is essential for the participant to continue the study.

Concomitant and rescue medication:

The participants will be instructed to inform the investigators before taking any type of medication apart from trial drugs. The investigators will record the details of medications and the reason for taking them in the CRF. In case of any medical emergency, the use of any rescue medication will be permitted and the same will be recorded in the relevant section of the CRF.

Data collection and documentation:

Before conducting the clinical study, the investigators and research team will be uniformly trained on Good Clinical Practice (GCP) protocol, trial-specific processes and documentation. The research team will collect the information and fill in the details in the CRF (see Table 1 for details) for each visit. All documented data will be checked regularly by the Principal Investigator (PI) to avoid

mistakes and omissions. Any modifications made shall be clearly visible, and the corrections shall be signed with a date by the PI. The data will be subsequently recorded in an e-format and verified as required; the original CRFs shall be archived in order with search catalog.

Statistical analysis:

All statistical data analyses will be performed using the SPSS 26.0 version software. Categorical data will be presented as numbers (percentage) and will be compared using the $\chi 2$ test/Fisher's exact test. Continuous variables will be described with either mean and standard deviation for data with normal distribution or median and interquartile range for non-normally distributed data. The within-group analysis will be done using a paired sample t-test for normal data, whereas the Wilcoxon signed-rank test will be used to compare non-normal data. Comparisons between the experimental and control groups at each time point will be done using an independent sample t-test or Mann–Whitney test for normal and non-normal data, respectively. A $P \leq 0.05$ will be considered statistically significant.

Monitoring:

The monitoring committee constituted by the sponsor will conduct on-site or virtual monitoring to ensure adherence to trial protocol, compliance to GCP and CCRAS Research Policy.

Trial audit:

The regulatory authorities, the Institutional Ethics Committee, or the funding agency will audit the trial, and the investigators will ensure access to all the documents related to the study for the on-site audit.

Ethics and dissemination:

The study is approved by the IEC of NARIP vide letter no. 8/16/23/NARIP/Tech meeting/2511, dated 31 March 2023, and has been registered prospectively at the Clinical Trial Registry of India (CTRI/2023/09/057330). The study will be conducted in accordance with the ICMR National Ethical Guidelines for Biomedical and Health Research on Human Participants (2017). Written informed consent (English & Malayalam) will be obtained from the eligible participants before screening. All protocol modifications will be communicated to the IEC and funding agency, and accordingly, it will be corrected in the CTRI. The CRFs will be stored in a secure area, and the participant's data will be coded to ensure confidentiality. The study participants will be given routine medical care if required,

after the completion of the study period. The study outcomes will be disseminated through research articles in peer-reviewed scientific journals and presentations at national conferences.

Discussion:

Several conventional conservative and surgical treatments have been evaluated over the last few decades in the management of chronic fissure in ano. [7] Presently available medical therapies including topical steroids, local anesthetics and bulk laxatives have considerable success rate in healing acute anal fissure, but their limited efficacy in treating chronic anal fissure has lead to selection of surgical procedures. [8,9] But concerns over the rates of incontinence after surgery have forced medical community to explore new pharmacological methods of treating chronic anal fissures safely and effectively. [10, 11] Ayurveda has advocated a systematic and effective management strategy for both exogenous and endogenous ulcers. *Murivenna* oil is one among the various medicated oil which are administered effectively by the Ayurvedic physicians for various ulcers of traumatic and pathological origin. As per Ayurvedic texts, anal fissures have to be managed in the principles of traumatic wound treatment. *Susrutha Samhitha*, a comprehensive text book on surgical and parasurgical practices of Ancient India has advocated oil irrigation/infiltration to pacify *Pitta dosa* which is considered pivotal in the pathology of inflammation and wound formation. [12] The drugs used for the preparation of *Murivenna* oil, namely *A. vera, P. glabra, B. hispida, A. racemosus*, and *M. oleifera* are *Pitta samaka* (pacifying pitta) and *Vranavasadana* (reduce the hypergranulation of wounds). Further they are proven to have analgesics and anti-inflammatory properties. [13] Murivenna can potentially help to pacify the pain, spasm and promote healing of the anal fissure.

Triphala choornam which is also prescribed in the interventional group of the study possess multidimensional actions. [14] The formulation not only acts as a laxative but also helps in wound healing owing to its antimicrobial and debridement property. [15]

Trial registration:

Clinical Trial Registry of India (CTRI/2023/09/057330)

Trial status:

The trial is currently has been started at National Ayurveda Research Institute for Panchakarma, Thrissur, Kerala, India and is in recruitment phase.

Financial support and sponsorship:

The CCRAS, Ministry of Ayush, Government of India is funding the study. The funding agency also provided technical support in study design and development of the study protocol.

Access to data:

The funding agency, i.e., CCRAS, will have access to the final study data.

Author's contributions:

- Conceptualization & Writing - Original Draft: KMPS, Methodological support: IP, PB, AKR & AA, Writing - Review & Editing: SJ, Protocol Review & Administrative support: BCS, NS & RA

Conflicts of interest:

The authors declare that they have no known competing interests.

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Appendix A

Supplementary file 1: SPIRIT checklist.

Supplementary file 2: Consort form and patient information sheet.

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Supplementary Files

CONSORT (or other) checklists

Consort Checklist.
URL: http://asset.jmir.pub/assets/1b263f7571bc6b50549ad030d531dc71.pdf