AYURVEDIC MANAGEMENT OF FISTULA IN ANO: A SYSTEMATIC REVIEW PROTOCOL

KM Pratap Shankar¹, GN SreeDeepthi², Rohit KS³, GK Swamy⁴

ABSTRACT

Introduction: Fistula in ano is considered to be complicated and vicious due to its nature of recurrences and exacerbations. Ayurveda includes this disease under the list of AstaMahagada (eight serious diseases that are difficult to treat by nature itself) due to this attribute. Ayurvedic literature offers various effective and safe management strategies for fistula in ano. Several works have been conducted to prove the efficacy and effectiveness of various treatment modalities mentioned in Ayurvedic texts. Kshara sutra, Kshara karma, Agnikarma, and Ksharavarti are a few to name in this list. A lacuna exists in not analyzing or compiling these works. Hence, the purpose of this systematic review is to generate evidence for efficacy, effectiveness, and safety profile of Ayurvedic interventions in the management of fistula in ano.

Materials and methods: Electronic search from various online databases and clinical trial registers will be done. Manual search for gray literatures will be done from various colleges and universities. There will be no language restrictions. Three authors independently will screen all citations and abstracts to identify potentially eligible trials. Based on the inclusion criteria, full articles will be evaluated and disagreements will be discussed among the three authors. Data extraction from the included studies will be done by the three reviewers independently with extraction forms containing methods, participants, interventions, comparators/controls, and outcomes. Each of the included trials will be assessed for risk of bias. Primary data analysis will be done for both qualitative and quantitative data. Heterogeneity among trials will be assessed by inspecting forest plots. If heterogeneity is detected, and it is still considered clinically meaningful to combine studies, a random-effects model will be used. Meta-analysis will be done for pooled estimates and others would be presented as narrative synthesis and shall be represented in tabular and graphical forms.

Dissemination: The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and in print. The review may guide healthcare practices and policy framing regarding the treatment of fistula in ano with Ayurvedic interventions.

Study registration: PROSPERO registration no. CRD42019131911.

Keywords: Ayurveda, Ayurvedic management, Bhagandara, Fistula in ano, Kshara Sutra, Systematic review, Systematic review protocol.


BACKGROUND

Fistula in Ano: Modern Perspective

Fistula in ano is a common surgical anorectal anomaly; it is notorious due to its chronicity, recurrences, and frequent exacerbations. Prevalence of anal fistula in European population is estimated as 1.69 per 10,000.¹ A study conducted among the Indian rural population estimated the incidence of low anal fistula around 8.6 per 1 lakh population with male to female ratio as 11.2:1.² Another study reported that anal fistula constitutes 1.6% of all surgical admission in India.³ The fistula tract connects the primary openings with one or more secondary openings and becomes fully manifested upon spontaneous or surgical opening of perianal/rectal abscess. The disease is characterized by one or more external openings in the perianal region with an apparent internal opening anywhere in the anorectal mucosa. Pus discharge associated with mild to severe pain will be the presenting feature. Majority of cases will be having recurrent formation of abscess with spontaneous decompression. The goals in the treatment of an anal fistula are to eliminate the primary fistula opening, any associated tracts, or any secondary openings without a change in continence.⁴ The simplest anal fistulae are treated using fistulotomy with a high rate of recurrences and other morbidities. Complex fistulae management poses increased risk of a change in continence and higher chances of recurrences which forced the surgeons to search for a better option. Various modalities like cutting seton, advancement flap, fibrin glue injection, fistula plug, ligation of intersphincteric fistula tract (LIFT), or BioLIFT (LIFT technique with a variation) are being tried to overcome the hardship faced by the patients.

Interventions for Fistula in Ano: Modern Perspective

Complex anal fistulae managed with cutting seton have demonstrated a recurrence rate of 0–8%, with minor and major incontinence as 34–63% and 2–26%, respectively.⁵–⁸ Advancement flap that is considered as the gold standard treatment of complex fistulae, demands high-technical knowledge, and has minor or major incontinence rate as 31 and 12%, respectively.⁹,¹⁰ Fibrin glue is easy to apply, but due to its liquid consistency, it fails to fix within the tract; and uncertainty of tissue growth in to the glue explains its reason for poor outcome and disappointing long-term effects.
results.11 Anal fistula plug gained instant favor due to its simplicity, ease of performance, lack of disturbance to surrounding tissues, and high patient tolerance rate. But studies with long follow-up has reported that healing rates are below 50%, with some as low as 24%.12 Recently LIFT technique has gained acceptance among the surgeons due to its advantages such as preservation of sphincter, minimum damage to tissues, faster healing time, and comparatively easy to perform. However, the indication is limited to transphincteric fistulae, and larger studies with longer follow-ups are still lacking in substantiating the benefits.

Various modalities presently available are unsatisfactory with high recurrence rate and risk of incontinence. To combat such a critical ailment, a comprehensive approach with definitive and positive outcome has been advocated through Ayurveda.

Fistula in Ano: An Ayurvedic Perspective

Bhagandara (NAMC code ED-16) mentioned in Ayurvedic texts is the condition equivalent to fistula in ano. Early details of the condition are available from Charakasamhita which are mentioned in the context of Swayathu.13 Later on Susrutha in his treatise Susrutha Samhita has given a detailed description about Bhagandara. Bhagandara is mentioned as the one among the “AstaMahagada” (eight serious diseases that are difficult to treat by nature itself).14 According to him, the condition is called Bhagandara because they break through the Bhaga (perineum), Guda (anus), and Basti (bladder regions). Further he adds that those without an opening are called Bhagandara-pidaka (anorectal abscesses) and those with an opening are called Bhagandara (fistula in ano).15 Susrutha explains five types of Bhagandara: Satapakana, Ustragriva, Parisariva, Sambukavarta, and Unmargi. The etiology, pathogenesis, clinical features, nature of discharge, pain, the sequelae, and complications of all types of Bhagandara have been given in detail.16 Vagbhata, the author of Astanga Hridaya, has followed Susrutha in his description, with slight difference in the classification. He describes eight types of Bhagandara in detail. In addition to the above five types, he has added Parikshepi, Riju, and Arsobhagandara.17

Interventions for Fistula in Ano: An Ayurvedic Perspective

Ayurveda, describes about the preventive and curative aspects in the treatment of Bhagandara. Prevention of suppuration of abscesses and recurrent formation are explicitly described. Nidanaparivarjana (avoidance of etiological factors) and various conservative procedures are mentioned.18 On failure of medical management, various surgical and parasurgical procedures are to be done to treat the condition. Susrutha has described explicitly the surgical procedure to be undertaken for each type of Bhagandara. The tract after probing has to be “laid open,” and the internal opening identified is cut by the knife; or else, Agnikarma (type of parasurgical procedure in which thermal cauterization of tissue or body part is done akin to moxibustion) or Kshara (caustics) should be applied. This is the general surgical procedure for all types of Bhagandara.19 Ksharasutra (medicated seton) is mentioned as the treatment of choice for Bhagandara by Charaka and Vagbhata.13,20 Susrutha has mentioned Ksharasutra in the management of Nadivrana (sinus) and Bhagandara.21 Although the preparation of Ksharasutra is not available in the earlier texts, later texts like Chakradatta and Rasatarangini have mentioned the details.22,23 Ksharavarti is a type of plug prepared from caustic medicines, and it is indicated in the treatments of Nadivrana and Bhagandara.21

How the Intervention might Work

Ksharasutra destroys the wall of the fibrotic fistulous tract by Ksara24 (destroying) property of Kshara. The resultant inflammation in the tract causes necrosis of fibrous tissue. Fibroblastic proliferation forms fibrin network and helps in healing by promoting the formation of granulation tissues.25 The same mechanism can be expected in Agnikarma and Kshara karma of the fistulous tract. The mechanical pressure exerted by tying the Ksharasutra in the tract will cut the tissues and helps in natural healing. The ingredients present in the Ksharasutra preparation demonstrate antibiotic effects, which cure the local infection and promote good healing.26 The drugs of the Ksharasutra are easily delivered to the local tissues; they dissolve in to the tissue planes and heal the numerous microscopic offshoots of the fistulous tract and thus preventing recurrences. As the cutting of tract by the Ksharasutra is a slow process, the tissue gets sufficient time for proper healing, thus preventing damage to the sphincters and change in continence.

Why it is Important to Perform this Review?

Ksharasutra application is stated in Ayurvedic text as a treatment of Bhagandara (fistula in ano) and is becoming universally accepted as a safe, simple, and sure treatment of fistula in ano. Ksharavarti (medicated caustic plug) and Agnikarma (therapeutic cautery) are also commonly practiced. An optimal treatment of anal fistula should be one that is associated with low recurrence rate, minimal incontinence, and a good quality of life. Most clinical studies and reviews undertaken in Ksharasutra and other Ayurvedic interventions tried to prove this advantage over other conventional treatments. Till date, no systematic reviews are undertaken to evaluate the efficacy and complications of Ayurvedic treatments in fistula in ano. The importance of this review is to highlight the advantages of Ayurvedic interventions in fistula in ano to public domain.

OBJECTIVES

• Systematic review of the clinical data in view of efficacy, effectiveness, and morbidity of Ayurvedic interventions in the management of fistula in ano.
• Meta-analysis of the clinical data in view of efficacy, effectiveness, and morbidity of Ayurvedic interventions in the management of fistula in ano.

MATERIALS AND METHODS

Criteria for Selection of Study

Types of Study to be Included

Randomized controlled trials (RCTs), quasi-experimental trials, single-group clinical trials comparative clinical trials, pragmatic trials, and review papers on management of fistula in ano with Ayurvedic interventions will be screened for data analysis.

Types of Participants

The trials with patients fulfilling the diagnostic criteria based on symptomatology of Bhagandara explained in Ayurvedic classics and patients with primary anorectal fistula proven clinically or by imaging will be included. The trials with patients of secondary fistula and complex fistula and also trials done with immune-compromised, HIV-infected, or uncontrolled diabetes patients will be excluded.
Types of Interventions
Interventions: The studies with Kshara sutra or Ksharavarti or Agnikarma or Ayurvedic internal medications as treatment of fistula in ano/Bhagandara will be included.

Comparators/Control
Surgical procedures such as fistulotomy, excision, and primary repair with an anorectal myomucosal advancement flap, cutting and noncutting setons (irrespective of the materials used), and other methods of treatment (marsupialization, radiofrequency ablation) for fistula in ano will be considered as comparators.

Outcome Measures
Primary Outcome
- Clinical healing of fistulous tract with absence of pain and discharge
- Proportion of participants developing a recurrence of up to 2 years defined as an abscess spontaneously discharging or requiring surgical drainage, or a recurrent fistula either at the same site or at a different site within 2 years

Secondary Outcome
- Immediate postoperative complications such as pain, bleeding, and infections
- Development of incontinence defined by incontinence scores (its impact on quality of life and specific problems such as use of pads, soiling, urgency, flatus, liquid stool, and solid stool)

Search Methods for Identification of Studies
Electronic Search
The following electronic databases: PubMed, Cochrane Library (Cochrane Central Register of Controlled Trials: Issue 6 of 12, June 2018), AYUSH Research Portal (Govt. of India), DHARA (Digital Helpline for Ayurveda Research), Google Scholar, Ancient Science of Life, Shodhganga@INFLIBNET, and online clinical trial registers will be searched.

Manual Search
Manual search in central and departmental libraries of Govt. Ayurveda College, Trivandrum, NTRUHS, Vijayawada, IPGT and RA, GAU, Jamnagar and Ayurveda Research Database27 will be done to identify unpublished works. Head of the institutes will be contacted and permission to search from the libraries and database will be sought. Identified works will be collected, and the authors will be directly contacted and permission will be taken before extraction of data.

There will be no language restrictions. Studies published till date will be sought. The search will be rerun just before the final analysis and further studies retrieved for inclusion.

Data Collection and Analysis
Selection of Studies
Three authors (KMP, GNS, and KSR) will independently screen all citations and abstracts to identify potentially eligible trials. Full articles of potentially eligible trials will be obtained and independently evaluated for inclusion in the review based on the inclusion criteria (based on the type of study, participants, intervention, and outcome measures mentioned in criteria for selection of study). Disagreements will be discussed among the three reviewers. Blinding of report authors, journals, date of publication, and sources of financial support or results will not be done. The details of selection process will be shown in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (Flowchart 1).
Data Extraction and Management
Data extraction from the included studies will be independently done by three reviewers, with extraction forms containing the following specified characteristics:

- **Methods**: randomization procedure, concealment of allocation, blinding of outcome assessment, sample size calculation, and length of follow-up.
- **Participants**: classification of disease (low or high fistulae), number randomized, number completing follow-up, and reasons for withdrawal from the study will be analyzed.
- **Interventions**: Ksharasutra or Ksharavarti or Agnikarma or Ayurvedic internal medications
- **Comparators/control**: surgical procedures like fistulotomy, excision, and primary repair with an anorectal myomucosal advancement flap, cutting and noncutting setons (irrespective of the materials used), and other methods of treatment (marginalization, radiofrequency ablation).
- **Outcomes**:
  - Efficacy/effectiveness: Clinical healing of tract (including the unit cutting time and healing of tract)
  - Recurrence, and at what time frame in each intervention.
  - Morbidity:
    - Immediate postoperative complications like pain, bleeding, and infections
    - Anal functional disturbance (incontinence).

Data extraction from the included studies will be independently done by three reviewers, with extraction forms containing the following specified characteristics:

If disagreement persists and data extraction is found difficult from published results, clarification will be taken from the authors of the trial. Format of data extraction sheet is attached as Annexure 1.

Assessment of Risk of Bias in Included Studies
Two authors (GNS and KSR) will independently assess the risk of bias in the included trials. KMP will independently check these assessments. Attempt will be made to contact the trial authors if details are missing in the publications or are unclear. Disagreements will be resolved through consensus. Each of the included trials will be assessed for risk of bias in the following domains: sequence generation, allocation concealment, blinding (separately assessed for blinding of participants and personnel and for blinding of outcome assessors), incomplete outcome data, selective outcome reporting, and other biases (relating to particular aspects of study design and conflicts of interest). For each of these components, a judgment will be assigned between the authors regarding the risk of bias of high, low, or unclear. The judgments will be recorded and justifications in “risk of bias” tables accompanying the characteristics of the included studies will be analyzed and findings will be summarized in a risk of bias summary graph and figure.

Measures of Treatment Effect
**Data Analysis**
Both qualitative and quantitative data as collected from various sources shall be considered for primary data analysis. In cases where pooled estimates can be obtained, the systematic review will be followed by a meta-analysis (based on the homogeneity of the RCT); others would be presented by narrative synthesis and shall be represented in tabular and graphical form. The analysis of the systematically collected data shall be conducted by R software. Dichotomous data will be presented and combined using relative risks, continuous data will be summarized by arithmetic means and standard deviations, and data will be combined by using weighted mean differences; and both will be accompanied by 95% confidence intervals. Medians and ranges will be reported in tables. Arithmetic means and standard deviations will be used to summarize continuous data, when the data are assumed to be normally distributed. Separate summary effect estimates will also be generated for studies that meet and do not meet the individual quality criterion. Heterogeneity among trials will be assessed by inspecting forest plots, looking for overlapping confidence intervals, applying the Chi-square test, with a p value of 0.05, indicating statistical significance, and using the I² test with a value of 50% to denote moderate levels of heterogeneity. If heterogeneity is detected, and it is still considered clinically meaningful to combine studies, a random-effects model will be used. A sensitivity analysis will be done to investigate the robustness of the results to the quality components, provided there are sufficient trials. A funnel plot will be utilized to indicate publication bias, heterogeneity of results, or differences in the methodological quality.

Managing Missing Data
Original authors will be requested to provide the missing data whenever possible. If not possible, the available data will be analyzed.

Subgroup Analysis and Investigation of Heterogeneity
If significant heterogeneity is detected, and if data permit, attempts will be made to explore the reasons for heterogeneity in the following subgroup analyzes:

- **Duration of fistula in ano:Bhagandara (less than 6 months; 6 months to 2 years; more than 2 years).**
- **Type of Bhagandara (types according to Susruta Samhita and Astanga Hrdaya).**
- **Type of fistula in ano (high anal or low anal/intersphincteric or transphincteric or extraspshincteric or suprasphincteric or submucosal).**
- **Type of Ksharasutra or Kshara or Ksharavarti or conservative medicine.**
- **Baseline severity (high disease activity vs moderate to low disease activity) as assessed by scores, using a valid instrument to report disease activity.**
- **Duration of follow-up (less than 6 months; 6 months to 12 months; more than 12 months).**

Sensitivity Analysis
If data permit, attempts will be made for sensitivity analysis to investigate the robustness of the results for the primary outcomes and secondary outcomes by excluding trials at high risk of bias, excluding studies with imputed data and skewed data. If heterogeneity is assessed to be not significant for any outcome (see data analysis), the data will be reanalyzed using a fixed-effect model, since the random-effects models assign more weight to smaller studies with more variance and yield more conservative results.

Ethical Considerations
Ethical clearance has been obtained from Institutional Ethical Committee. A voluntary, signed, witnessed informed consent shall be obtained from the institutes/practitioners for sharing the unpublished data.
Systematic Review Registration
The study has been registered in PROSPERO (PROSPERO registration no. CRD42019131911).

Conclusion
The systematic review will be published in a peer-reviewed journal. It will also be disseminated electronically and in print. The review will be updated, and a GRADE evaluation of the quality of evidence will be conducted to provide summaries of the future state of the evidence for the efficacy of Ayurvedic interventions in fistula in ano. The review may guide healthcare practices and policy framing regarding the treatment of fistula in ano with Ayurvedic interventions.

Acknowledgments for Methodology of the Systematic Review with Significant Changes Suitable for the Current Setting
We acknowledge Director General—CCRAS, Deputy Director General—CCCRAS, and Director and Asst. Director (Ay.), NARIP, Cheruthuruthy for their immense support and encouragement throughout the preparation of protocol.

Acknowledgment for the methodology of the systematic review with significant changes suitable for the current setting.


References

Annexure 1: Data extraction sheet

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हिंदी सारांश

भगदर के प्रबंधन में आयुर्विदिक चिकित्सा: सिस्टेमेटिक रिव्यू प्रोटोकॉल
kे एम प्रताप शंकर, जी एन श्रीदिवसी, रोहित के एस, जी के स्वामी

परिचय: भगदर को पुनरावृत्ति और अतिरिक्त की प्रकृति के कारण पर्याप्त और कष्टदायक माना जाता है। इस विशेषण के कारण आयुर्विद में यह ‘अष्टमहाद्व’ की सूची (आठ गंगीर बीमारियों जिनका इलाज किया जाता मुश्किल है) में शामिल है। भगदर के लिए आयुर्विदिक साहित्य विभिन्न प्रभावों और सुसंपत्त प्रबंधन प्रदान करता है। आयुर्विदिक यंत्रों में उल्लिखित विभिन्न उपचार विधियों की प्रभावकारीता और सुसंपत्त को साबित करने के लिए कई अध्ययन किए गए हैं। इस सूची में कुछ नाम शार्म सूत, शार्म कर्म, अन्नकर्म और शारणर्ति हैं। इन कामों का विशेषण या संकल्प किया जाने में अभी कभी है। इसलिए प्रस्तुत अध्ययन का उद्देश्य भगदर के प्रबंधन में आयुर्विदिक चिकित्सा की प्रभावकारीता, प्रभावशीलता और रूपण के लिए प्रमाण निर्माण करना है।

विधी और विश्लेषण: विभिन्न ऑनलाइन डेटाबेस और नैदानिक परीक्षण रजिस्टर से इलेक्ट्रॉनिक खोज की जाएगी। ये साहित्य के लिए हस्तचारित खोज विभिन्न कॉन्फ्रेंस और विश्वविद्यालयों से की जाएगी। भाषा पर प्रतिबिंदु नहीं होगा। तीन लेखनों द्वारा स्वतंत्र रूप से संबंधित ग्रंथ परीक्षण की पहचान करने के लिए सभी उद्धरणों और सार की जांच की जाएगी। समावेश ग्रंथों के आधार पर, पूर्ण लेखों का मूल्यांकन किया जाएगा और तीन लेखनों के बीच असहमति पर चर्चा की जाएगी। सम्मिलित अध्ययनों से डेटा निष्कर्षण तीन समीक्षकों द्वारा स्वतंत्र रूप से तैयार, प्रतिबांधियों, हस्तक्षेपों, तुलनात्मक/निराल्प्रक्षण और परिणामों वाले निष्कर्षण प्रप्तियों के साथ किया जाएगा। पूर्ववर्ती खंड के लिए शामिल परीक्षणों में से प्रत्येक का मूल्यांकन किया जाएगा। प्रभावित डेटा विश्लेषण गुणात्मक और मजबूत डेटा दोनों के लिए किया जाएगा। फॉरेस्ट प्लाट का निरीक्षण करके परीक्षणों के बीच विषमता का मूल्यांकन किया जाएगा। यदि विषमता का पता लगाया जाता है और इसे अभी भी अध्ययनों को सशोभित करने के लिए नैदानिक रूप से सार्थक माना जाता है, तो एक हस्तक्षेप प्रबंध वाले मॉडल का उपयोग किया जाएगा। 'पूर्व' किया गए अनुमानों के लिए मेटा-प्लान्सिस किया जाएगा और अन्य अनुमान वर्णनात्मक संस्करण के रूप में प्रस्तुत किए जाएगे और सारणीबद्ध और विषमता रूप में विश्लेषित किया जाएगा।

प्रस्ताव: व्यस्तित समीक्षा एक समकक्ष समीक्षा की तरीका पर प्रकाशित किया जाएगा। इसे इलेक्ट्रॉनिक और पिच में भी प्रसारित किया जाएगा। यह समीक्षा आयुर्विदिक हस्तक्षेप के साथ भगदर के उपचार के विषय पर स्वास्थ्य सेवा कार्यों तथा नीति निर्धारण का मार्गदर्शन कर सकती है।

सिस्टेमेटिक रिव्यू प्रोटोकॉल प्रमाणकरण: इस अध्ययन का पंजीकरण PROSPERO (PROSPERO पंजीकरण सं. - CRD42019131911) में किया गया है।