Journal of Pharmaceutical Research International

33(60B): 12-18, 2021; Article no.JPRI.80032
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Comparative Evaluation of the Efficacy of Hydrocortisone Suppository and *Durvadi gudavarti* in *Raktarsha*: A Management Protocol

Biswas Nitin [a≡#*], Jajoo Suhas [bφ#], Jaiswal Reena [a†#] and S. R. Kapse [c⊦]

[a] Department of Shalya Tantra, Mahatma Gandhi Ayurveda College, Hospital and Research Centre, Salod, Datta Meghe Institute of Medical Sciences, Wardha, Maharashtra, India.
[b] Department of Surgery, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Sawangi Meghe, Wardha, Maharashtra, India.
[c] Department of Computer Technology, Yeshwantrao Chavan College of Engineering, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i60B34579

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/80032

Study Protocol

Received 10 October 2021
Accepted 16 December 2021
Published 21 December 2021

ABSTRACT

The most common diagnosis for any anorectal complaint particularly of rectal bleeding in adults is haemorrhoidal disease. Regardless of grading conservative treatment is used primarily in symptomatic haemorrhoids. In Ayurveda, *Sthanik Chikitsa* (Local application) in the management of *Arsha* (Hemorrhoids) includes *pralepa/pratisaran* (Paste application). Instead of applying the *lepa* in the clinics by the clinician/proctologist, those formulations could be developed into *Gudavarti* (traditional suppository) & used in the management of *Raktarsha* (bleeding piles) for better compliance. Hence, development of '*Durvadi Gudavarti'* using the indigenous medicinal herbs mentioned in Charaka Sanhita (Classical Ayurveda text) for *pratisaran/pralepa* in *Raktarsha* & its efficacy will be evaluated.

Objectives: To study & compare the efficacy in patient treated with standard- Hydrocortisone suppository group & interventional- *Durvadi Gudavarti* group in the management of *Raktarsha* (Bleeding piles).

[≡] *PhD Scholar;*
[φ] *Professor;*
[†] *Associate Professor;*
[#] *Dr.;*
[⊦] *Assistant Professor*
**Corresponding author: E-mail: dr.biswas84@gmail.com;*

Methodology: 130 patients of 2nd grade hemorrhoids will be selected and will be allocated into two equal groups by computer randomization. Experimental group will be treated with *Durvadi Gudavarti* & control group with Hydrocortisone based suppository for 2 weeks. Following Symptoms- PR Bleeding, Anal Pain, Prolapse of Pile mass/Lump, Anal pruritus, Mucous discharge & Constipation will be assessed subjectively and Size/ (Volume in cubic millimeter) of pile mass will be the objective parameter for study. Clinical evaluation will be done at Baseline and 3rd, 5th, 10th, 15th day after treatment onset. Proportion of patients that would respond clinically on 10th day will be the main end point, determined via disappearance of the clinical symptoms & more than or equal to 50 % reduction in the initial size of pile mass/lump. Time to response & need for any oral/ parenteral medication for pain, bleeding and constipation would be the secondary variables. Side effects (type, duration & severity) will be registered carefully.
Expected Results: *Durvadi Gudavarti* contains indigenous herbs having anti-inflammatory, analgesic, haemostatic, wound healing, astringent, & laxative properties. Hence, it is expected to be as efficacious as Hydrocortisone suppository with lesser side effect in the management of *Raktarsha.* Results will be assessed on the basis of clinical assessment criteria using proper statistical values and tools. Changes will be observed in objective outcomes.
Conclusion: *Durvadi Gudavarti* will be efficacious in the management of *Raktarsha.*

Keywords: Raktarsha; hemorrhoids; Gudavarti; suppository; bleeding PR.

1. INTRODUCTION

Background: Presently, one of the most common ills of man is considered to be hemorrhoids. The most common diagnosis for any anorectal complaint particularly of rectal bleeding in adults is haemorrhoidal disease [1]. At least one out of two in the western world over the age of 50 years has formation of some degree of haemorrhoids as suggested by Goligher in 1967. It seems to have more prevalence in rural Indians than in Africans, Black and white Americans & Western Europeans. With the progressive adoption western way of life it became more common. The cost to the community is reduction in working time & economical loss due to which it is considered to be a major health hazard [2]. Very few articles have been there regarding the epidemiology of hemorrhoids, therefore the prevalence of hemorrhoids is not well documented, it range between 4.4 to 5% worldwide [3].

Rationale: Majority of symptomatic haemorrhoids are treated conservatively, but for cases with pronounced symptoms surgery may be considered [4]. Primarily haemorrhoidal illness is managed using conservative measures like dietetic, Hygienic, life style changes, and symptomatic treatment. Along with oral medication, topical administration of ointments/ suppositories containing corticosteroids (eg. hydrocortisone) and anaesthetics (e.g. lidocaine) is widely used & probably most useful in clinical practice. It gives fast local relief from pain, itch, bleeding & discomfort [4,5]. However, these ointments/suppositories are not free from side effects like rectal ulcerations, burning sensation, skin/mucosal atrophy, contact dermatitis, telangiectasia & also there is limitation in duration of administration (not more than 2-4 weeks is advisable) [6].

Thus there is a need of the effective and safe herbal medicine for topical administration in hemorrhoids. Application of *lepa*/medicinal herbal paste (*Haridradi lepa, Pipalyadi lepa, Shuranadi lepa*) or *Ksharkarma*/Caustic therapy in clinics/operating rooms for the management of *Raktarsha* (bleeding piles) is clinician/ proctologist dependent procedure, So those formulations could be developed into *Gudavarti* (traditional suppository) so that patient himself can administer it at home so as to save time, money & for better compliance as well. Hence, this study is proposed to evaluate the efficacy of newly developed '*Durvadi Gudavarti'* using the indigenous medicinal herbs mentioned in Charaka Sanhita (Classical Ayurveda text) for *pratisaran/pralepa* in *Raktarsha* & compare it with standard hydrocortisone base suppository. So, single blind (Participant blind) double arm Randomized reference standard controlled clinical trial will be conducted. It will be a interventional study for equivalence hypothesis testing of two parallel group with 1:1 allocation ratio.

2. AIM AND OBJECTIVES

Aim: Development of a better treatment modality & dosage form in the management of *Raktarsha.*

Objectives:

- To study the efficacy of Hydrocortisone suppository in the management of *Raktarsha*.
- To study the efficacy of *Durvadi Gudavarti* in the management of *Raktarsha.*
- To compare the efficacy of Hydrocortisone Suppository and *Durvadi Gudavarti* in the management of *Raktarsha*.

Case Definition: Diagnosed case of Internal grade 2 haemorrhoids (Goligher classification) patient of either sex between the age group 20 to 60 years characterized by bleeding PR, anal pain, pile mass/lump possibly of red-violet/blue color appearance, anal pruritus, mucous discharge and constipation.

Research question: Whether *Durvadi Gudavarti* is as efficacious as Hydrocortisone Suppository in *Raktarsha*?

Research Hypothesis

Null hypothesis (H_0): There is difference in efficacy of Hydrocortisone suppository and *Durvadi Gudavarti* in *Raktarsha.*

Alternative hypothesis (H_1): There is no difference in efficacy of Hydrocortisone suppository and *Durvadi Gudavarti* in *Raktarsha.*

3. METHODOLOGY

Trial design: Single blind (Participant blind) double arm Randomized reference standard controlled clinical trial. It is an interventional study for equivalence hypothesis testing of two parallel group with 1:1 allocation ratio.

Study setting: The study will be conducted in academic hospital MGACH & RC, Salod (H), Wardha, Maharashtra, India.

Sample Source: This study will be performed at the DMIMS Mahatma Gandhi Ayurveda College Hosdpital and Research Centre, Salod, Wardha, M.S, India. The patients needed for study will be selected from the OPD of Department of *Shalyatantra* in the above said hospital.

Drug source: Raw drugs required for preparation of *Gudavarti* will be collected from local market, will be identified in *Dravyaguna* Department and preparation of *Gudavarti* will be done in *Rasashastra & Bhaishyajyakalpana* Department of MGAMC, Salod, Wardha, M.S.

Hydrocortisone based suppository (Corect/ Anomex Suppository) is available in local medical stores; that would be purchased and provided to the patient.

Composition of *Durvadi Gudavarti* (Trial drug): *Durva swarasa (*Cynodon dactylon)*, Yashtimadhu churna* (Glycyrrhiza glabra)*, Daruharidra churna (*Berberis aristata*, Sarjarasa churna (*Vateria indica Linn.)*, Nimba churna (*Azadirachta indica)*, Manjishtha churna (*Rubia cordifolia)*, Shatadhout ghrita (*Butyrum Departum) & Guda (*Jaggery).

Hydrocortisone based suppository: Composition – Hydrocortisone (0.25% w/w) + Zinc oxide (5% w/w) + Lidocaine/Lignocaine (3% w/w) + Allantoin (0.5% w/w).

Registration Number: REF/2021/04/043081, the registration number for this trial is under process.

4. ELIGIBILITY CRITERIA

Inclusion Criteria:

- Patients of 20 to 60 Years of age of either sex.
- Diagnosed case of internal grade 2 haemorrhoids (Goligher classification) patient (characterized by bleeding PR, anal pain, pile mass/lump possibly of red-violet/blue colour appearance, anal pruritus, mucous discharge and constipation).
- Patients having hemoglobin more than or equal to 10 gm%.
- Patient who will give written, informed consent to participate.

Exclusion criteria:

- Patient of below the age of 20 and above age of 60.
- Patient having hemoglobin less than 10 gm%.
- Grade 1, 3 and 4 Haemorrhoids (Goligher classification), external haemorrhoids, external thrombosed haemorrhoids. Haemorrhoids associated with acute Fissure-in-Ano, Fistula in ano, Ulcerative colitis, Crohn's disease, Malignancy, Intestinal Polyps, Diverticulitis.
- Patients of TB, Diabetes mellitus and uncontrolled hypertension, portal hypertension, septic or severe

hemorrhagic complications, bleeding disorders, acute diarrhoea in last 12 hours, on corticosteroids therapy or have allergy to corticosteroids, on anticoagulant medications, planning for any surgical procedure for haemorrhoids or taking other antihaemorrhoidal drugs.

- Pregnant & nursing female.
- HIV and HbsAg positive patients.
- Those who are not consenting for conservative management

Laboratorial investigations: HB, RBS, BT/CT, HIV, HBsAg.

4.1 PT(INR) and Liver Function Test

Procedure/Intervention – After taking the written informed consent**,** on 1st day of treatment demonstration to the patient and/or close relative of patient will be done regarding procedure of medicine administration. Patient will be advised to lie down in left lateral position. Interventional drug (Suppository/*Gudavarti)* will be gently inserted in anal canal about 1 *inch*, ensuring sufficient lubrication with Glycerine/*Ghrita.* Then patient will be asked to lie down for a minimum period of 10 minutes in same position.

From 2nd day up to the 2 weeks of treatment period patient will be advised to administer by self at home after defecation twice daily (12 hourly).

Criteria for discontinuing or modifying allocated interventions: Subject will be withdrawn from the study if development of severe drug reactions, profuse bleeding, or occurrence of any other serious illness happens, the subjects will be provided free treatment till recovery.

Table 1. Intervention table

Group	Experimental group	Control group
Sample size	65	65
Intervention	*Durvadi Gudavarti*	Hydrocortisone suppository
Dose	1 *Gudavarti* BD (12 Hourly)	1 Suppository BD (12 Hourly)
Visits for evaluation	3rd, 5th, 10th & 15th day after treatment onset	3rd, 5th, 10th & 15th day after treatment onset
Total Duration of treatment	2 weeks	2 weeks
Follow up	1st & 2nd week after end of intervention	1st & 2nd week after end of intervention

Sample size (N) = 130

Sample size formulae for Two-sided equality hypothesis testing for two parallel sample proportion designs:

$H_0 = \theta_1 - \theta_2 = 0$ *versus* $H_1 = \theta_1 - \theta_2 \neq 0$

$$n_1 = \frac{(Z_{\alpha/2} + Z_{\beta})^2 [\, r\,\theta_1(1-\theta_1) + \theta_2(1-\theta_2)\,]}{(\theta_1 - \theta_2)^2}$$ [7,8]

$n_2 = rn_1$

Here r = 1 for equal size $n_1 = n_2$

$$n_1 = \frac{(1.96 + 0.84)^2 \times (0.24+0.22)}{(0.25)^2} = \frac{7.84 \times 0.46}{0.06} = 60.15$$

$n_1 = n_2 = 60$, considering 5% drop out rate = Total 6, 3 in each group = 63

Round up to 65 samples needed in each group. Total sample size, N = 130

Table 2. Variables and descriptions for sample size calculation

Variables	Descriptions
α	Two-sided significance level = 0.05
1-β	Power of the test = 0.80
θ_1	Expected success proportions of Experimental group = 0.42
θ_2	Expected success proportions of Control group = 0.67 [9]
θ_1- θ_2	The difference between the true mean response rates of experimental group and control group = 0.25
R	Ratio of sample size of control group to experimental group = 1
n_1	Sample size of experimental group = 65
n_2	Sample size of control group = 65
N	Total sample size = 130

Statistical Analysis: The following descriptive and inferential statistics will be used in the statistical analysis: Chi-square test, one-way ANOVA, and multiple comparisons: Tukey test & software for analysis is SPSS 26.0 Version & graph Pad Prism 7.0 Version and $P < 0.05$ is considered as level of significance. Results will be reported as per CONSORT guidelines.

Criteria for Assessment: [9]

- **Objective Criteria:** Size/ (Volume in cubic millimeter) of pile mass. Anoscopy using anoscope & measurement of pile mass will be done using calibrated millimeter rulers.
- **Subjective Criteria:** PR Bleeding, Anal Pain, Prolapse of Pile mass/Lump, Anal pruritus, Mucous discharge & Constipation.

Subjective Parameters viz. *Gudagat Raktstrava* (PR Bleeding), *Guda Shool* (Anal pain), *Arshaankur Prachiti* (Prolapse of lump/pile mass), *Guda Kandu* (Itching), *Gudagata Picchilata* (Mucous Discharge) and *Vibandha* (Constipation) will be assessed:

- Qualitatively as Yes/No and
- Frequency will be measured quantitatively as Never/>2days apart/every day or alternate day.
- Severity of Anal pain will be assessed using linear visual analogue scale (VAS) – range 0-10 (0- no pain and 10- worst pain, it will be regrouped as mild: 1-3, moderate: 4-6 & severe: 7-10) [9,10].
- Severity of PR Bleeding will be assessed subjectively as: No bleeding, Mild bleeding - Found in toilet paper/Fingers, Moderate bleeding- Few (~ 01-10) drops/Dripping, Severe- Splash of blood/Sluice [11].

Clinical evaluation will be done at Baseline and 3rd, 5th, 10th, 15th day after treatment onset.

Primary Outcome: Proportion of patients that would respond clinically on 10th day will be the main end point, determined via disappearance of the clinical symptoms & more than or equal to 50% reduction in the initial size of pile mass/lump.

Secondary Outcome: Time to response & need for oral/parenteral medication for pain, bleeding and constipation will be secondary variables.

Side effects (type, duration, severity) will be recorded. Severity of side effects will be classified as: 1- mild, if no therapy or only topical treatment would be sufficient, 2- moderate, if a specific oral medication would be needed; and 3- severe, if hospitalization and/or parenteral medication would be required.

Groupings: Two groups, Group A- Experimental Group (EG) & Group B- Control Group (CG).

Allocation: Allocation of the patients in two different groups will be done by computer generated random number method. (Allocation ratio- 1:1).

Allocation sequence & enrolment of participants will be done by PI & assignment of participants to interventions & blinding them by the PI & Co supervisor. Both the medicament will be provided to the participants in an identical packing.

5. DATA COLLECTION, MANAGEMENT, AND ANALYSIS METHODS

Data collection methods: Case registration form with detailed history and examination i.e. Case Record Form (CRF).

Consent form in English, Hindi.

	Q1	Q2	Q3	Q4	Q5	Q6
Enrolment of Patients						
Medicine preparation						
Data collection						
Writing thesis parts up to Methods						
Data analysis						
Writing rest of thesis						
Submission						

Fig. 1. Gantt Chart (in quarterly based)

NOTE: The study highlights the efficacy of "ayurveda" which is an ancient tradition, used in some parts of India. This ancient concept should be carefully evaluated in the light of modern medical science and can be utilized partially if found suitable

Assessment of objective criteria & subjective parameters will be recorded.

Data of all participants will be collected and reported in case sheet form.

Patients will be in touch by means of telephone calls and timely advice for medication.

Patients Visits and follow up findings data of the patient will be recorded.

Data management: The data entry coding will be done by PI & co-supervisor.

Dissemination policy: The data information will be disseminated by paper publication, authorship eligibility guidelines, and any other competent writer's intended use.

6. DISCUSSION

Raktarsha (Bleeding Piles) causes complications like anemia & needs to be managed immediately. The cause of bleeding according to Ayurveda parlance is increase *pitta dosha* which involves the *rakta dhatu* & cause bleeding from *bahirmukh strotas* (external orifices). So, *stambhan* (haemostatic) treatment is to be done after *pachana* of *dosha*. For *stambhan* effect the drug should have *Tikta &/or Kashaya ras, Sheet virya*, & *Madhur vipak. Durvadi Gudavarti* contains indigenous herbs having all these properties. It has anti-inflammatory, analgesic, haemostatic, wound healing, astringent, & laxative properties. It would reduce the varicosity of the hemorrhoidal veins due to *tikta, kasaya ras* and astringent property, reduce the swelling due to anti-inflammatory property, and due to its laxative property it would reduced the amount straining while defecation. Hence, it is expected to be as efficacious as Hydrocortisone suppository with lesser side effect in the management of *Raktarsha.* Few of the related studies were reviewed [12-14].

Translational Outcome:

- The positive outcome of this study would provide better efficacious therapeutic modality with lesser side effect as compared to widely used corticosteroid based suppositories.
- Patients can be obtained for the newly developed *Durvadi Gudavarti*. Patients who are often reluctant to surgery, who can't visit clinic frequently for procedures like *Ksharkarma, lepa/pratisaran* in the management of *Raktarsha* would be benefited.

7. CONCLUSION

Conclusion will be drawn by suitable analysis of data.

CONSENT

Before the research begins, the patient's written informed consent will be obtained. Every patient's privacy will be protected & confidentiality will be maintained during the study.

ETHICAL APPROVAL

Research ethics approval; approval from research ethics committee has been taken. Ref. No. MGACHRC/IEC/July-2020/43, dated- 28-07-2020.

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/80032