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Original Research Article

Outcomes of additional local antibiotic to local analgesic and vasodilator in acute anal fissure - A randomized controlled study

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ABSTRACT

Background: Acute anal fissure is a common and painful condition of ano-rectal region characterized by tear in the anoderm causing pain during defecation. Mainstay of its treatment is pharmacotherapy with lifestyle modification.
Objective: Current study was undertaken to evaluate the role of add-on local antimicrobial in recovery and relief of symptoms of acute anal fissure in comparison to local anesthetic and vasodilator without any antimicrobial.
Materials and Methods: It was a randomized, assessor-blinded, active-controlled clinical study in which data of 68 eligible participants were analyzed. Participants of both group received local lignocaine and nifedipine and the test group (Group B) received metronidazole ointment in addition. Healing was assessed by clinical examination and pain by Numeric Pain Rating Scale. Sample size was calculated based upon result of older pilot study and the proportion of recovery were assessed by Chi-square test.
Results: After 6 weeks of treatment, 61 out of 68 (i.e., 89.7%) patients receiving add-on antimicrobial recovered completely compared to 75% of the comparator group. Reduction of pain and cessation of bleeding were also significantly better in patients receiving additional antibacterial.
Conclusion: Healing and symptom relief in acute anal fissure is better with addition of local antibacterial along with local vasodilator and anesthetic.

1. Introduction

Anal fissure is a common disease of anorectal region, encountered in surgical out-patient department.[1] It is a very painful condition and affects the quality of life. Typically, fissures cause cyclical pain that occurs during defecation and persists for a few hours afterwards.

Anal fissures are an elliptical or longitudinal tear in the anoderm distal to the dentate line, exactly proximal to or at the level of the anal verge.[2] It is termed acute or chronic depending on the duration of symptoms.[3] Although the exact etiology is not known but the contributory factors postulated are tight anal sphincter, sphincter spasm, ischemia, infections, trauma due to passage of hard stool and also due to acute diarrhea, pregnancy and other medical conditions.[3]

On examination the finding classically are spasm of the internal sphincter. This is mainly responsible for the pain during defecation. The sphincter spasm is possibly due to ischemia.

In majority of cases anal fissures are located in the posterior midline as the blood supply to this area is the least.

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The first line treatment for anal fissures is conservative. This includes smooth muscle relaxants like nitroglycerines and calcium channel blockers in addition to general measures like fiber rich diet and Sitz bath. These help in reducing the internal sphincter tone. Local anesthetic and steroid containing gels are prescribed along with laxatives to reduce symptoms and further local trauma.[4,5] If these measures fail then surgical treatment is performed which is lateral anal sphincterotomy.[4,6,7] The treatment for chronic non responding fissures is lateral anal sphincterotomy (LIS). LIS can lead to permanent sphincter defect and minor fecal incontinence in around 10% of cases. The recurrence rate after sphincterotomy has been reported to be around 16%.

Anal canal is a region with bacterial concentration and fissures in this region are prone to infection and addition of antibiotic might be helpful in the healing process. Metronidazole is a 5-nitroimidazole derivative antibacterial with a lipophilic character. Its bactericidal effect is particularly effective on anaerobic pathogenic bacteria. It is widely used in clinical practice for the treatment of ailments where mixed pathogen microorganisms are predominant. The objective of undertaking the current study was to investigate whether the addition of local antibiotic containing metronidazole is helpful in reduction of the symptoms and improvement of the recovery process in patients for anal fissure.

2. Materials and Methods

2.1. Study design and participants

This was a prospective, randomized, open label, assessor and analyst blinded, parallel arm, active controlled clinical study conducted on 136 consenting participants with acute anal fissure in the department of General Surgery, Indira Gandhi Institute of Medical Sciences, Patna, in between August 2019 to July 2021. The patients in the age group of 18 to 70 years who were clinically diagnosed for acute anal fissure after clinical examination by consultant surgeon, suffering not more than 6 weeks, lesions involving epithelium only, complaining of pain associated with ulcers, were eligible to be included in the study. Pregnant and/or lactating mothers were excluded. Patients with associated co-morbidities such as chronic obstructive pulmonary disease (COPD) or asthma, hypertension, coronary artery disease, diabetes mellitus (DM), HIV/AIDS, inflammatory bowel disease or those who did not give consent were excluded from the study. Patient was also excluded if any history of hypersensitivity to intervention medicines or previous history of any drug related problems was revealed.

The study protocol was approved by Institutional Ethics Committee (IEC). All patients were informed in details about the research study, provided with participant information sheets (PIS) about the study and were given chance to ask questions and clarify doubts if any. Only the eligible voluntary patients were recruited after obtaining a written informed consent. The study was registered with Clinical Trial Registry of India (CTRI/2021/04/032801)

2.2. Sampling and sample size

All consecutive patients attending the OPD were screened and approached for informed consent. Participants with acute anal fissure were allocated into two study arms of this study by simple random sampling. Based on the difference of proportion of healing rate over 6 weeks reported in previous study on acute anal fissure the effect size was estimated to be 16%.[8] Presuming 95% confidence interval with 80% power and 5% chance of type 1 error sample size was estimated to be 108 for two groups. Assuming 20% attrition rate the total sample size was 136. Sample size was calculated with OpenEpi software version 3.1.[9,10]

2.3. Randomization and allocation concealment

After screening eligible and consenting patients were assigned into two groups as per allocation sequence by simple randomization. The allocation sequence after randomization was generated by blinded statistician and the sequence was concealed in sequentially numbered sealed opaque envelopes by a Senior Resident of different unit of same department who was not a part of this study. The Senior Resident with the help of a Pharmacy staff prepared the numbered cartons in which the medicines as per randomization sequence was put and sealed. Participants, investigators and study-related personnel were masked to treatment group allocation until the group allocation process is complete and medicine cartons are dispensed. The unit head (Additional Professor) who was the outcomes assessor did clinical examinations of all participants and was blinded to allocated treatment till the end of the study. The data analyst was also blinded.

2.4. Study arms and interventions

There were two groups namely group A (comparator) and B (test) into which patients were randomized. Patients in group A (comparator group) received 2% lignocaine gel with 0.2% nifedipine ointment to be applied locally in anus and circumferentially in perianal margin with applicator three times daily for 6 weeks. In group B (test group) metronidazole 1% ointment was added to 2% lignocaine gel with 0.2% nifedipine ointment and to be applied locally in anus with applicator three times daily for 6 weeks. All patients irrespective of group allocation were advised Seitz bath with lukewarm water two times daily and lifestyle modification including intake of plenty of oral fluid and high fiber diet. In addition lactulose, a laxative, was prescribed 15 mL two times daily to all to keep stool soft.

2.5. Study procedure

Patients attending the Surgery OPD of IGIMS with symptoms suggestive of anal fissure were screened by on-duty doctors and eligible patients who agreed verbally to participate in the study were assessed for inclusion/exclusion criteria. The eligible potential participants were informed in details about the study by the junior consultant (co-investigator) and informed consent obtained. Then the participants were assigned to one of the study groups as per the allocation chart by a resident who was not an investigator. For further clinical assessment the participant was referred to the principal investigator (additional professor) who was masked to the group allocation. After that all patient-reported parameters (pain, bleeding, etc) were assessed by suitable tool and noted. Then patient received the medicine box labeled only as 'A' or 'B' as per allocation and the on-duty nurse and pharmacist guided the patient with appropriate use of medicines and other methods (like, Seitz bath). Patients were assessed first after 1 week of starting treatment and then after 3 weeks and 6 weeks of medication. They were informed to communicate at any time over phone in between the visits if needed. The study activity is expressed by Consort flow diagram [vide Figure 1]

2.6. Outcomes

Epithelization or scar formations within 6 weeks were considered healed and primary end point was proportion of patients achieving complete healing of the acute anal fissure within 6 weeks of treatment. Degree of healing of the fissure was noted at all visits and. Pain assessment was done at all visit using the 11-item Numeric Pain Rating Scale (NPRS). Improvement in bleeding was assessed by comparing proportion of participants without bleeding in two groups. Improvement in other symptoms such as discharge and pruritus were assessed using the numeric rating score (NRS).

2.7. Statistical analysis

Individual data were collected in case record form and then all data were tabulated in MS Excel Worksheet. Demographic data were presented as percentage. Distribution of data of each variable was tested by Shapiro-Wilk test and Q-Q plot. Pain score as per numeric rating scale was compared in between treatment groups by Mann–Whitney U test. Proportion of patients with complete healing or no bleeding status was compared by Chi-Square test. The method of analysis was modified intention-to-treat (mITT) in which at least one follow-up data were carried forward for analysis. Data were analyzed using SPSS version 21.

3. Results

Among the participants with acute anal fissure, in Group A 38 (27.94%) were males and 30 (22.06%) were females; whereas in Group B 36 (26.47%) and 32 (23.53%) were males and females respectively. Most of the patients (63.97%) (41 in Group A and 46 in Group B) were young adults (18 – 45 years). In each of the two groups 68 patients participated. There was no statistically significant difference among the two groups in terms of mean age, gender, intensity of pain, bleeding status, pruritus, and incidence of diarrhea or constipation. The most common complaint among both groups was pain and bleeding during defecation. All the patients completed at least one follow-up visit out of the 6 weeks treatment and no adverse effects or reactions were reported.

Complete recovery of the fissure with healing was evident as early as 3 weeks after initiation of treatment. After 3 weeks significantly higher proportion of participants who got add-on antimicrobial i.e., Group B (23 out of 68) recovered compared to Group A (11 out of 68). By the end of 6 weeks significantly higher proportion of patients who got add-on antimicrobial (Group B, 61 out of 68; i.e., 89.7%) recovered compared to Group A (51 out of 68; i.e., 75%) [$].

At presentation, there was no significant difference in between mean Numeric Pain Rating Score (NPRS) in between the study groups, 7.86 + 0.968 in Group A compared to 8.62 + 0.912 in Group B (p= 0.1713). The participants receiving add-on antimicrobial in Group B had a significantly lower pain score compared to Group A. The difference in the mean NPRS score became statically significant from 3^{rd} week onwards (p = 0.024 after 3 weeks and 0.025 after 6 weeks of treatment) [Table 2].

At presentation, there was no significant difference between bleeding per rectum in between two treatment groups (66 in Group A compared to 67 in Group B). But as early as 1 week after treatment bleeding responded better to treatment with add-on antibacterial as in Group B. After 1 week of treatment 16 out of 67 patients in Group B compared to 6 out of 66 patients in Group A reported cessation of bleeding. Both the treatments seemed to affect bleeding positively as after 3 weeks all 67 patients in Group B and 60 out of 66 patients in Group A (p = 0.033) reported cessation of bleeding per rectum [Table 3].

The mean numeral rating score for various symptoms like discharge and pruritus was comparable in both groups and resolved by 6 weeks of treatment.

Association with constipation or diarrhea was variable in two groups and no significant difference was noted.

4. Discussion

Anal fissure is a highly prevalent and highly discomforting disease. It is equally prevalent in both the sexes but due to

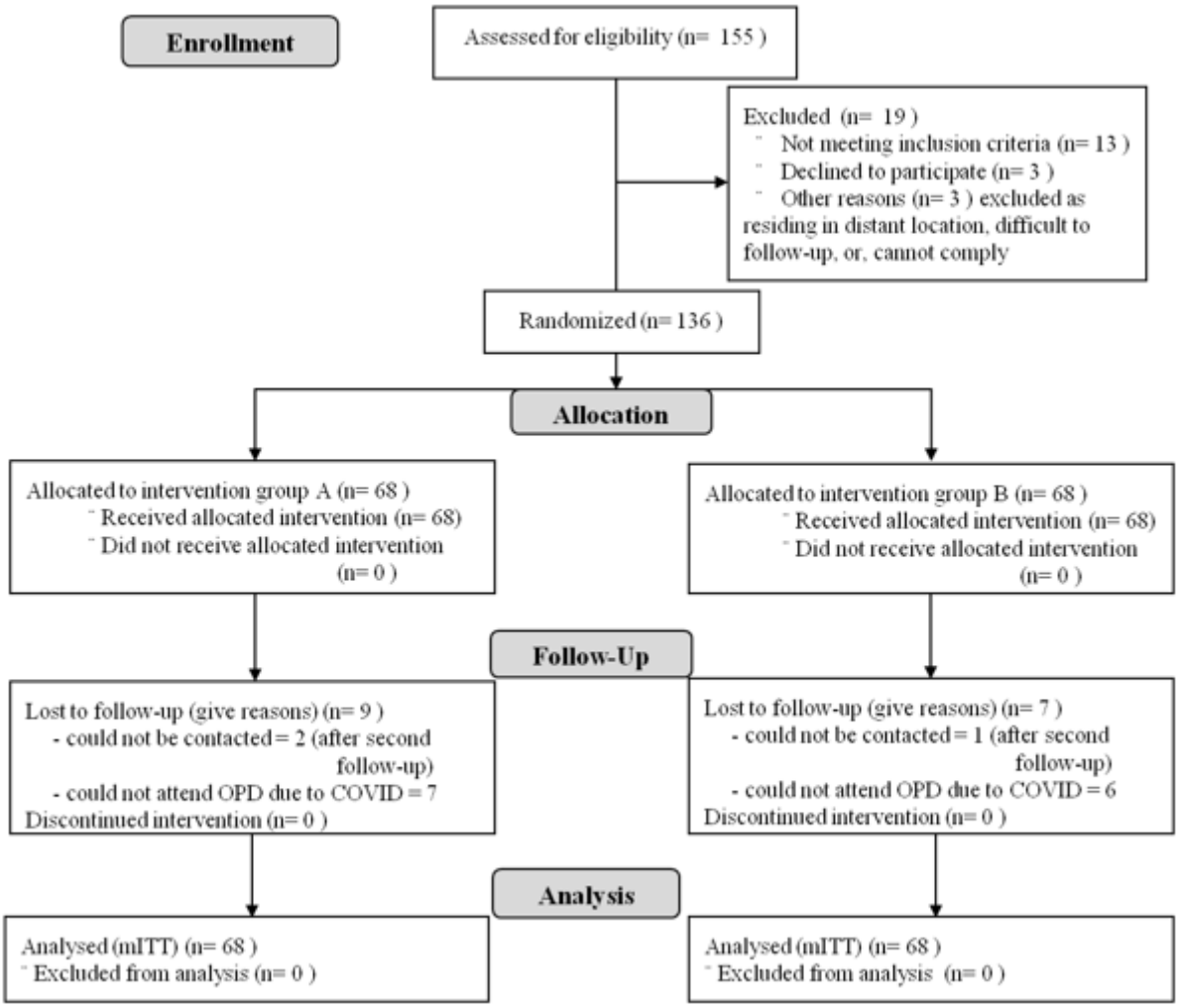

Fig. 1: Consort flow diagram of study activity mITT = Modified intention to treat analysis.

Table 1: proportion of participants with complete healing in different time periods after initiation of treatment

Follow-up after	Gr A (n=68)	Gr B (n=68)	P value	RR	95% CI
1 week	0	0	-	-	-
3 weeks	11	23	0.0285	0.5789	0.3455 – 0.9698
6 weeks	51	61	0.0414	0.6429	0.4635 - 0.8916

Chi-Square test

Table 2: Mean along with StandardDeviation of NPRS score for pain in two treatment groups during different visits before and after treatment

Visits	Gr A	Gr B	P value	95% CI
Baseline	7.86 + 0.968	8.62 + 0.912	0.171	0.426 – 1.174
1 week	4.84 + 0.976	4.52 + 0.974	0.0244*	1.238 – 2.301
3 weeks	2.33 + 1.654	1.82 + 1.326	0.326	0.873 – 1.306
6 weeks	1.77 + 1.325	1.29 + 0.986	0.025*	1.057 – 1.535

Mann- Whitney U test, *significant difference between groups

Table 3: Proportion of participants with cessation of bleeding per rectum in different time periods after initiation of treatment

Follow-up after	Gr A (n=66)	Gr B (n=67)	P value	RR	95% CI
1 week	6	16	0.034	0.502	0..248 – 0.913
3 weeks	60	67	0.0285	0.5789	0.345 – 0.969
6 weeks	66 (100%)	67 (100%)	-	-	-

Chi-Square test

sociocultural reasons women present later to a doctor than males. The typical symptoms of anal fissures are bleeding and proctalgia.[11] Pain is usually sharp that increases on passing stool. Fissure bleeds are usually bright red and small in amount.[12] As reported in literature our patients too presented with pain and bleeding during defecation and constipation.

In anal fissures the rupture occurring at the anoderm causes internal sphincter spasm, thus increasing the anal canal resting pressure leading to pain and decreased blood flow to the region. The continuous vicious cycle of pain, spasm and ischemia lead to chronic anal fissures. This knowledge lead to the use of local anesthetic agents in treatment of fissures. Local lignocaine is widely used for anal fissures. Studies have demonstrated healing rates of 40 – 60% with the use of local lignocaine gels.[13] With almost half patients continuing to have symptoms had researchers thinking of other possible contributing factors to wound healing. Wound healing is impaired by ischemia and infection is a known fact. The bacterial flora of anal fissures gave been studied by researchers and found to be colonized by Gram positive or Gram negative anaerobic bacteria or Gram negative aerobic bacteria.[14] Grekova et al also documented that addition of topical metronidazole in those patients whose swab revealed presence of anaerobic bacteria, lead to rapid relief of spasm of anal sphincter and pain along with enhanced fissure healing (95.6 % healing rate compared with 70.8 % in the control group, p = 0.048).[15] In our study healing rate in participants receiving local antibiotic was 89.7% compared to that without antibiotic 75%.

Considering the bacterial flora reported in previous studies we included topical metronidazole in our study which has an effective spectrum against these bacteria. In our study we documented that addition of metronidazole ointment in the treatment regimen improved the recovery rates from 75% (in control/group A) to 89.7% (with add-on antimicrobial/ group B). This can be explained by the decline in bacterial flora due to the local metronidazole leading to better wound healing. The difference of recovery rates in the two groups at the end of 6 weeks are found to be statistically significant with p value of 0.041 and 95% CI 0.463 - 0.891.

The proportion of patients with cessation of bleeding was significantly high in Group B with add-on antimicrobial. Karapolat B also reported similar finding after adding local antibiotic for the treatment of acute fissure.[8]

Controlling the local infection leads to reduction in inflammation and lowering the sphincter spasm. This in turn will lead to lowering pain and has been demonstrated in our study by the comparison of NPRS. Patients receiving add-on antimicrobial has significantly better relief of pain. The decrease in NPRS score became statically significant as early as 1 week after treatment. Findings of a pilot study documenting the advantage of local application of povidone-iodine solution in chronic anal fissures corroborates with that in our study.[15] Other authors have recorded the benefits of oral ciprofloxacin with or without metronidazole for a treatment period of 5 days by recording symptomatic relief in more than 90% cases with chronic anal fissures.[16] Further, the local application of ornidazole cream for 3 months in addition to oral antibiotics lead to a cure rate of 90%.[17]

Thus the benefits of antibiotics (local/oral) in the treatment of anal fissures have been documented by many authors to reduce the symptoms as well as improve the recovery of patients with anal fissures.

5. Conclusion

Anal fissure is a common painful condition with various non-surgical and surgical methods of treatment. Surgical methods have complications and used only when the non-surgical methods have failed. In our study it is inferred that the addition of local metronidazole to local anesthetic and vasodilator medication leads to a faster improvement in symptoms and also improves the recovery rates.

6. Contribution of Individual Authors

Dr. K Gopal assessed the clinical parameters including healing of each participant and supervised overall study procedure, Dr. VK Roy and Dr. M Kumar conducted overall trial procedure and collected data, Dr. A Kumari, Dr. VK Roy and Dr. SS Roy had the research idea, did the literature review and prepared the protocol; Dr. SS Roy planned the randomization procedure, did the data cleaning, statistical analysis, wrote the manuscript

7. Conflict of Interest

The authors have no conflict of interest to declare

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None.

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