

Sucralfate plus Metronidazole ointment is as effective as Diltiazem ointment for treatment of acute fissure in ano – an open label randomized clinical trial

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ABSTRACT

Background and objectives. Fissure in ano is one of the most common colorectal diseases seen by surgeons in daily practice. Currently medical management is the first line therapy for treating acute fissure in ano. Apart from general measures, various drugs like nitrates and calcium channel blockers are also used for topical application. Recently topical application of sucralfate and metronidazole are being advocated for in the same way, although there isn't much evidence for their effectiveness. In this study we have compared the efficacy of sucralfate (7% and Metronidazole (1%) ointment to the most commonly used diltiazem (2%) ointment for healing in acute fissure in ano and control of pain.

Materials and methods. The present study was a randomized clinical trial with total 96 patients, 47 in the Sucralfate + Metronidazole group and 49 in the Diltiazem group. Both drugs were prescribed for 4 weeks in addition to general measures like sitz bath, laxatives and oral fluids. Patients were followed up at 2 and 4 weeks. Control of symptoms like pain, bleeding and healing of ulcers in both groups were assessed. Frequency or graphs were used for qualitative variables and Mean+/-SD for quantitative variables. Chi-square and t-test was applied for comparison of the two groups, and p-value <0.05 was taken for statistical significance.

Results. Most patients were male and belonged to age group 30-50 years. Most patients in both groups improved on conservative treatment. The difference observed in key outcome parameters like control of pain, bleeding and healing of fissure in both groups weren't found to be statistically significant. Sucralfate and Metronidazole didn't have any incidence of adverse effects and was cheaper in price compared to diltiazem ointment.

Conclusions. Sucralfate and Metronidazole was as effective as diltiazem in treating of acute fissure in ano and can be recommended if allergy and adverse reactions to diltiazem are encountered.

Keywords: anal fissure, Diltiazem, Sucralfate, Metronidazole

INTRODUCTION

Fissure in ano is one of the most common ano-rectal complaints patients present with to the surgical outpatient department and is defined as a tear in the anoderm below the dentate line [1]. Because the tear extends to below the dentate line which is sensate, it is frequently painful and the pain usually lasts for at least one to two hours after defecation. [2,3]. Currently acute fissure in ano is generally managed by conservative management while chronic fissures may require surgical intervention [4].

It is estimated that pain in acute fissure in ano is present in more than ninety percent of patients and

the pain which can be described as sharp and tearing in character, causes significant discomfort and anxiety to patients [5]. The painful tear in the anoderm causes involuntary spasm of the internal anal sphincter. This spasm in turn causes local vasoconstriction leading to ischemia in the ulcerated area causing non-healing. This non-healing causes persistence of pain, thereby ultimately precipitating a vicious cycle of pain, spasm and ischemia [6]. Conservative management is currently focused on breaking this vicious cycle for relief of symptoms and healing. This includes general measures like a warm sitz bath, which causes local vasodilatation, reduces ischemia and pain, avoiding constipation

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by stool softeners, fibre-rich diet and increasing consumption of oral fluids [2,5,6].

Nitrates and calcium channel blockers are among the class of drugs being used currently in the medical management of acute anal fissures [6,7]. Oral or topical application of these agents cause smooth muscle relaxation thereby decreasing the spasm and tone of the internal anal sphincter which in turn causes vasodilatation, therefore, decreasing acute pain, ischemia thereby promoting fissure healing. Among these glyceryltrinitrate, diltiazem and nifedipine have been most widely used and studied. These agents while effective [7], however, are not without their specific adverse effects. Glycertrinitrate (GTN) can cause severe headaches [8,9] and nifedipine is associated with headache and flushing in some patients [10-12].

Diltiazem [7,13-15] is one of the calcium channel blockers most widely in current practice due to its fewer adverse effects. Diltiazem is mainly used by the local application in the form of an ointment to reduce the incidence of systemic side effects.

Metronidazole, an antimicrobial highly effective against anaerobic microorganism is commonly used in management of various anorectal pathologies like abscess, fistula in ano etc. and is associated with significant reduction of perianal pain [16]. As such, metronidazole can be an effective medication for treatment of fissure in ano with regards to ulcer healing as well as pain reduction. Few studies [17,18] have shown beneficial role of metronidazole in anal fissures.

Sucralfate has long been known as antiulcer drug. Topical sucralfate is used in radiation proctitis [19] and recently is being evaluated for treatment of anal fissures with encouraging results [20].

Recently fixed dose topical combinations of metronidazole (1%) and sucralfate (7%) has been made available commercially for treatment of fissure in ano. This combination potentially has the benefits of both metronidazole and sucralfate through synergistic action. Although studies show that metronidazole and sucralfate individually are beneficial in management of fissure in ano, there has been no data to show whether this combination of these two drugs are as effective. Our current study was designed to determine whether combination of these two drugs is more effective over most commonly used topical diltiazem in ulcer healing and control of pain in acute anal fissures.

MATERIALS AND METHODS

This study was designed as a prospective randomized clinical trial and was conducted over a period of eighteen months at All India Institute of Medical Sciences Raipur which is a tertiary care teaching institute located in the state of Chhattisgarh, India. Clearance from institutional ethics committee was

taken. Informed consent was taken from all participants. Patients with acute fissure in ano presenting to the outpatient of department of general surgery were recruited. A total of 98 patients were enrolled in the study and were randomized into two groups with block size of four. Allocation concealment was done by SNOSE technique. One group (SM) was prescribed treatment with local application of metronidazole (1%) and sucralfate (7%) ointment and the other group (D) received diltiazem (2%) ointment. In both groups patients were advised to locally apply the respective ointments three times daily for a period of four weeks. All patients were advised conservative measures like sitz bath, laxatives and dietary advice. Patients were examined on OPD basis after 2 weeks of treatment initiation and at the end of 4 weeks. The primary outcomes were ulcer healing and pain assessed by Visual analogue scale. The CONSORT diagram is given in Figure 1.

Statistical analysis

Data analysis was done in SPSS-21 version software. Data presentation for qualitative variables was done in form of frequency or graphs. Data presentation of quantitative variables was done in form of mean \pm SD. Chi-square tests was applied for evaluation of qualitative data and t-test was applied for comparison of two groups. Consideration of p-value <0.05 for statistical significance.

RESULTS

A total of 98 patients were recruited into the study. Two patients in group SM were lost to follow up and after excluding there were 47 in SM (metronidazole + sucralfate) group and 49 in D (diltiazem) groups respectively whose data was analyzed. Most patients (38.5% n=37) were in the age group < 30 years followed by the age group 30-40 years (32.3%, n=31). More than 60% of the patients in both groups were male. Both the groups were well matched in terms of age, sex and BMI and there was no statistical difference between the two groups. The demographic parameters can be compared from Table 1.

Most of the patients in our study did not have any comorbidities presumably because most were in the younger age groups. The distribution of comorbidities can be seen in Table 2.

The most common presenting complaint was pain (95.8%) followed by constipation (66.7%) and then bleeding (55.2%). One fifth of patients also complained of pruritus. The distribution of complaints can be seen from Table 3 and Figure 2.

Majority of patients in both groups presented with a single fissure in ano (Table 4). However, nine patients in group SM and ten patients in group D had more than one fissure, although any other etiol-

CONSORT Flow Diagram

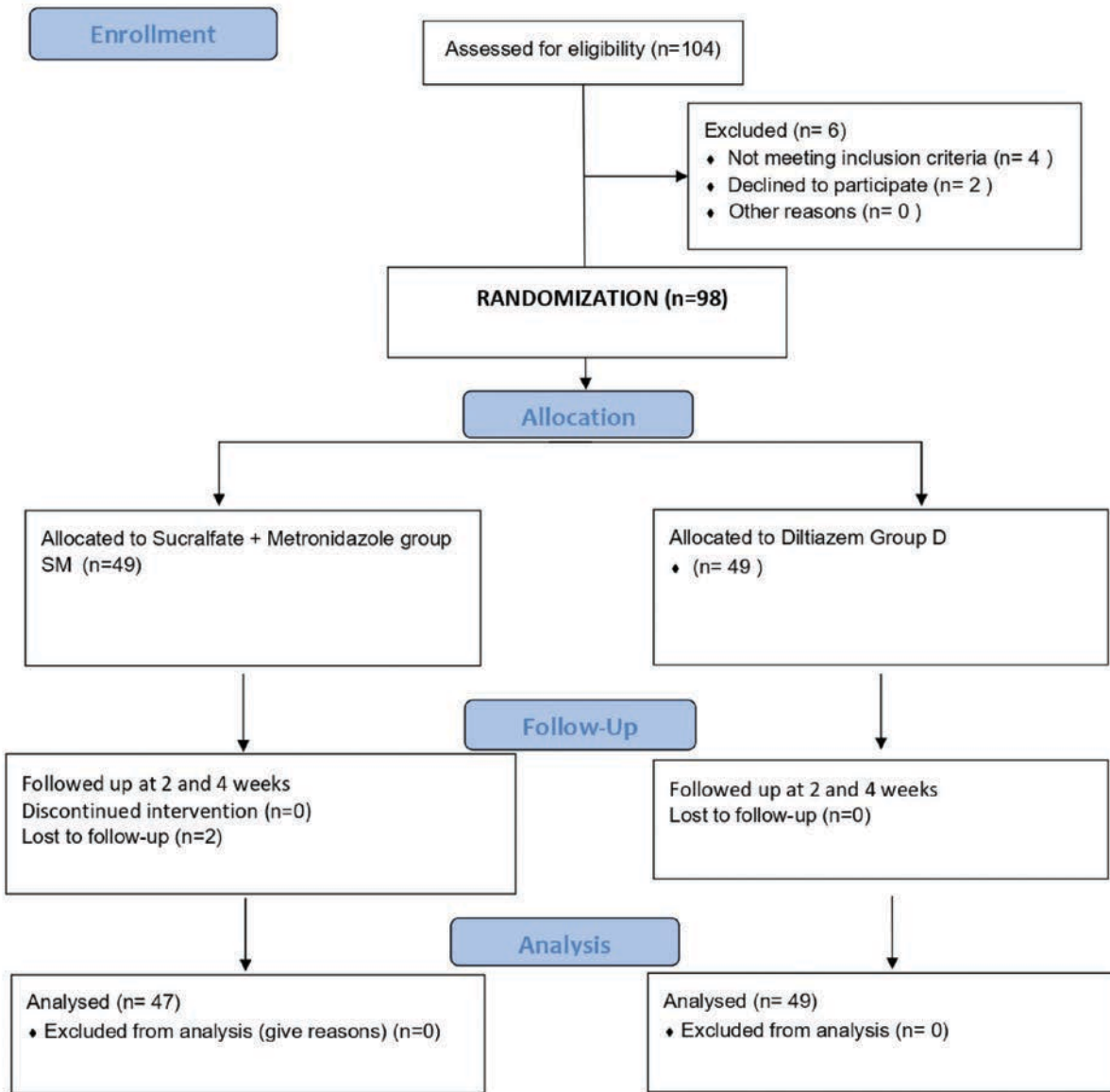


FIGURE 1. CONSORT Diagram

TABLE 1. Demographic variables

| Variables | Group SM (n=47) | | Group D (n=49) | | p value | |
|-----------------|-----------------|-------|----------------|-------|---------|------|
| | Mean | SD | Mean | SD | | |
| Age | 35.89 | 12.96 | 35.71 | 12.03 | 0.944 | |
| BMI | 24.94 | 2.93 | 24.15 | 3.05 | 0.198 | |
| Gender | n | % | n | % | 0.874 | |
| | Male | 29 | 61.7 | 31 | | 63.3 |
| | Female | 18 | 38.3 | 18 | | 36.7 |
| Age Group (yrs) | N=96 | | | | % | |
| <30 | 37 | | | | 38.5 | |
| 31-40 | 31 | | | | 32.3 | |
| 41-50 | 12 | | | | 12.5 | |
| >50 | 16 | | | | 16.7 | |

ogy was not found in those cases. The difference between the two groups was not significant.

After starting treatment, patients were followed up on outpatient department at 2 weeks and 4 weeks respectively to check for healing of fissure. At the end of 2 weeks the complete fissure healing rate were 34% vs 26.5% and at the end of 4 weeks 72.3% vs 77.6% in groups SM and group D respectively (Table 5). Although at 2 weeks more patients receiving sucralfate + metronidazole had healing of their fissures but at 4 weeks more patients in Diltiazem group were found to have their fissures completely healed. The difference in healing rates between the two groups was not found to be statistically significant.

TABLE 2. Distribution of comorbidities

| Comorbidities | | Group SM (n=47) | | Group D (n=49) | | Total (N=96) | | P value |
|-----------------------|-----|-----------------|-------|----------------|------|--------------|------|---------|
| | | N | % | N | % | N | % | |
| Hypertension | Yes | 6 | 12.8 | 2 | 4.1 | 8 | 8.3 | 0.124 |
| | No | 41 | 87.2 | 47 | 95.9 | 88 | 91.7 | |
| Diabetes | Yes | 1 | 2.1 | 1 | 2.0 | 2 | 2.1 | 0.976 |
| | No | 46 | 97.9 | 48 | 98.0 | 94 | 97.9 | |
| Hypothyroidism | Yes | 1 | 2.1 | 2 | 4.1 | 3 | 3.1 | 0.582 |
| | No | 46 | 97.9 | 47 | 95.9 | 93 | 96.9 | |
| Tuberculosis | Yes | 0 | 0.0 | 1 | 2.0 | 1 | 1.0 | 0.99 |
| | No | 47 | 100.0 | 48 | 98.0 | 95 | 99.0 | |
| Any other comorbidity | Yes | 3 | 6.4 | 5 | 10.2 | 8 | 8.3 | 0.89 |
| | No | 44 | 93.6 | 44 | 89.8 | 88 | 91.7 | |

TABLE 3. Distribution of patient complaints

| Complaints | | Group SM (n=47) | | Group D (n=49) | | Total (N=96) | | P value |
|---------------------------|-----|-----------------|-------|----------------|------|--------------|------|---------|
| | | N | % | N | % | N | % | |
| Pain during defecation | Yes | 45 | 95.7 | 47 | 95.9 | 92 | 95.8 | 0.966 |
| | No | 2 | 4.3 | 2 | 4.1 | 4 | 4.2 | |
| Bleeding per rectal | Yes | 26 | 55.3 | 27 | 55.1 | 53 | 55.2 | 0.983 |
| | No | 21 | 44.7 | 22 | 44.9 | 43 | 44.8 | |
| Pruritis | Yes | 16 | 34.0 | 10 | 20.4 | 26 | 27.1 | 0.133 |
| | No | 31 | 66.0 | 39 | 79.6 | 70 | 72.9 | |
| Constipation | Yes | 30 | 63.8 | 34 | 69.4 | 64 | 66.7 | 0.564 |
| | No | 17 | 36.2 | 15 | 30.6 | 32 | 33.3 | |
| Diarrhea | Yes | 0 | 0.0 | 1 | 2.0 | 1 | 1.0 | 0.325 |
| | No | 47 | 100.0 | 48 | 98.0 | 95 | 99.0 | |
| Alteration in bowel habit | Yes | 3 | 6.4 | 4 | 8.2 | 7 | 7.3 | 0.737 |
| | No | 44 | 93.6 | 45 | 91.8 | 89 | 92.7 | |

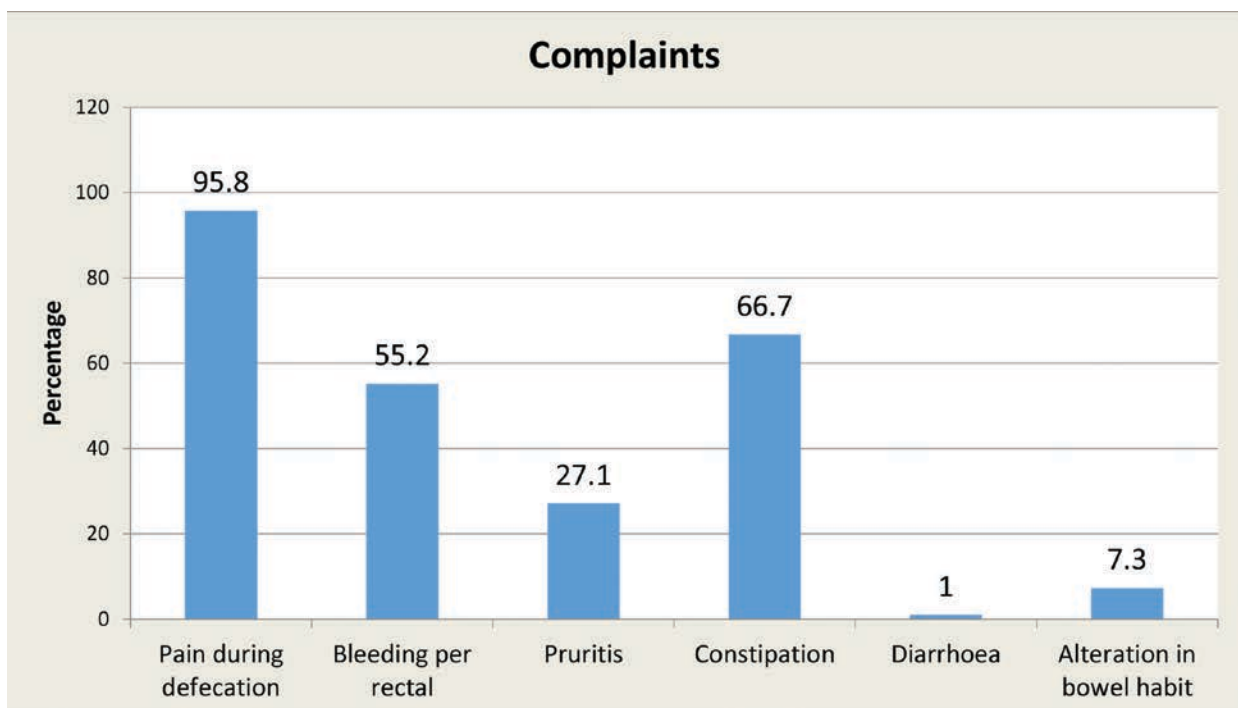
**FIGURE 2.** Distribution of patient complaints

TABLE 4. Number of fissures

| Number of fissures | Group SM (n=47) | | Group D (n=49) | | P value |
|--------------------|-----------------|------|----------------|------|---------|
| | N | % | N | % | |
| Single | 38 | 80.9 | 39 | 79.6 | 0.877 |
| Multiple | 9 | 19.1 | 10 | 20.4 | |

TABLE 5. Complete healed ulcer

| Complete healed ulcer | Day 1 | | 2 weeks | | 4 weeks | |
|-----------------------|----------|---------|------------|------------|------------|------------|
| | Group SM | Group D | Group SM | Group D | Group SM | Group D |
| Yes | 0 | 0 | 16(34.0%) | 13(26.5%) | 34(72.3%) | 38(77.6%) |
| No | 47 | 49 | 31(66.0%) | 36(73.5%) | 13(27.7%) | 11(22.4%) |
| Total | 47 | 49 | 47(100.0%) | 49(100.0%) | 47(100.0%) | 49(100.0%) |
| P value | --- | | 0.423 | | 0.556 | |

TABLE 6. Bleeding during defecation

| Complete healed ulcer | Day 1 | | 2 weeks | | 4 weeks | |
|-----------------------|------------|------------|------------|------------|------------|------------|
| | Group SM | Group D | Group SM | Group D | Group SM | Group D |
| Yes | 12(25.5%) | 10(20.4%) | 4(8.5%) | 6(12.2%) | 1(2.1%) | 1(2.0%) |
| No | 35(74.5%) | 39(79.6%) | 43(91.5%) | 43(87.8%) | 46(97.9%) | 48(98.0%) |
| Total | 47(100.0%) | 49(100.0%) | 47(100.0%) | 49(100.0%) | 47(100.0%) | 49(100.0%) |
| P value | 0.550 | | 0.549 | | 0.976 | |

TABLE 7. Comparison of pain

| Pain | Group SM (n=47) | | Group D (n=49) | | P value |
|------------|-----------------|------|----------------|------|---------|
| | Mean | SD | Mean | SD | |
| Day 1 | 5.38 | 2.09 | 6.08 | 1.94 | 0.093 |
| At 2 weeks | 3.06 | 2.22 | 3.06 | 2.27 | 0.995 |
| At 4 weeks | 1.38 | 1.80 | 1.97 | 2.19 | 0.149 |

Bleeding during defecation (Table 6) was one of the commonest reported complaints by the patients. Patients were asked about bleeding at enrolment and at 2 weeks and 4 weeks follow up. Almost all patients in both groups self-reported the complete stopping of bleeding by 4 weeks and the difference between the groups were statistically not significant.

Pain (Table 7, Figure 3) was the commonest chief complaint and pain was assessed by visual analogue scale at recruitment and then at subsequent follow ups. Mean pain scores calculated for both groups showed a steady decrease in pain and most patients had mild or no pain at the end of four weeks of therapy. There was no statistical difference in pain scores at the end of 2 weeks and 4 weeks.

DISCUSSION

At the present time, conservative therapy for acute

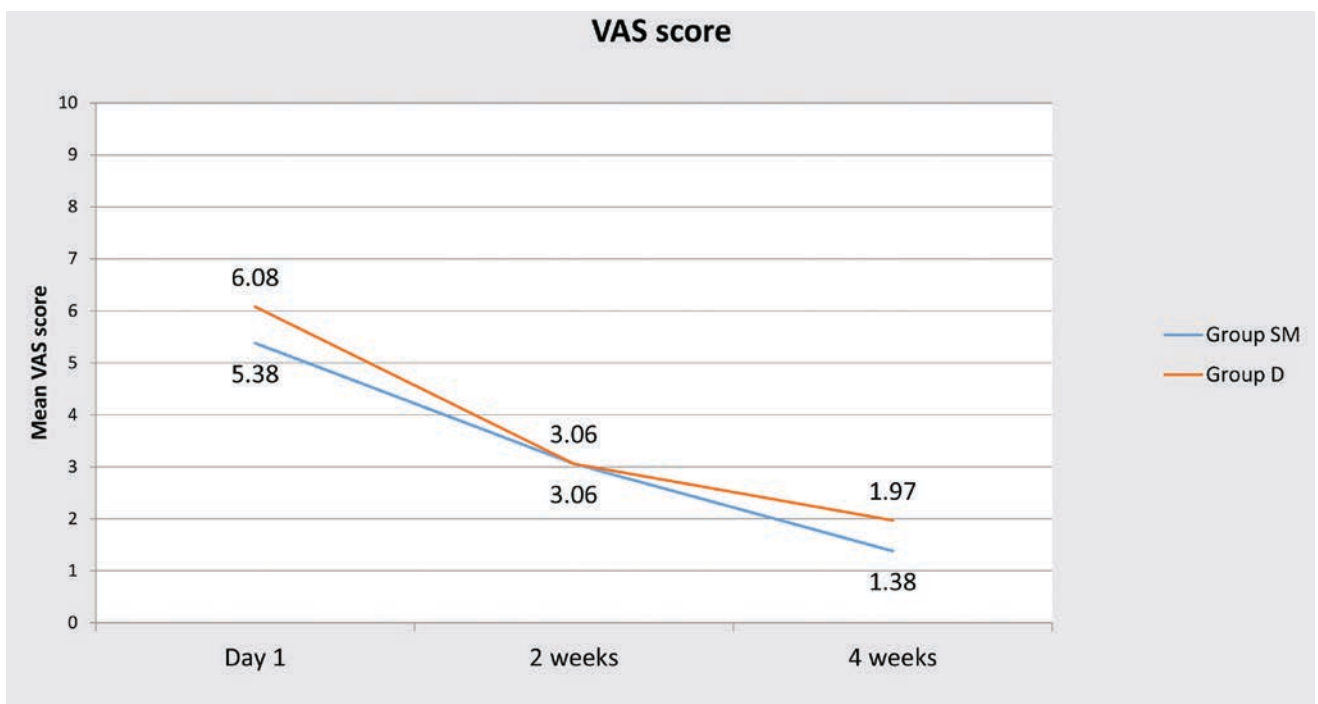


FIGURE 3. VAS Score

fissure in ano is the first line of treatment and accounts for healing of majority of such cases [5,21]. Surgical sphincterotomy although more durable with less recurrence rates still have a small but definite chance of anal incontinence [6,22] and is only considered for patients not responding to conservative therapy. In our current study, the effectiveness of topical application of sucralfate plus metronidazole against diltiazem in the treatment of acute fissure in ano was assessed. Due to its well-established effectiveness in treating acute fissure in ano, diltiazem was chosen as the standard agent to which the efficacy of sucralfate plus metronidazole were compared.

Most of the patients in our study were in the younger age groups and of male gender. Most studies however report almost equal incidence among males and females or even slight female preponderance [5,23]. This variation might be due to geographical and social factors. Pain, bleeding and constipation were reported as the most common complaints in our study which agrees with the studies reported from worldwide [1]. Almost all patients irrespective of treatment group reported the resolution of these symptoms at the end of four weeks which shows the efficacy of conservative management of this disease condition. Healing of the fissure ulcer was assessed at two weeks and at four weeks and healing was complete in more patients of the Diltiazem group compared to the SM group (38 vs 34). Although the difference was not found to be statistically significant, it clearly shows that topical application of diltiazem is quite effective and should be encouraged. Although diltiazem has lesser side effects than nitrates, sometimes rashes and itching can be a problem [5,24], and can lead to discontinuation of treatment. This adverse effect has not been observed with topical metronidazole or sucralfate so far.

The addition of topical antibiotic to therapy for anal fissure is quite an interesting proposition. Theoretically, antibiotics like metronidazole can help to control local infection which might directly or indirectly help in healing of any ulcer and reduce pain. Studies by Banu Karapolat [25] and Shahid et al. [18] also seems to support this theory but needs further investigation.

In our study pain was measured by VAS scoring at presentation, at 2 and 4 weeks respectively. Both the groups showed almost equivalent decrease in pain scores with time (Figure 2) and at the end of four weeks of therapy most patients had mild to no pain at all. This clearly shows that symptoms will resolve if ulcer healing is achieved whether by relaxation of sphincteric smooth muscle by calcium channel blockers and vasodilatation or by ulcero-protective agents like sucralfate. Apart from attaching to surface protein of ulcer such as albumin and fibrinogen to form stable insoluble protective barrier, sucralfate also prevents of release of cytokines and stimulate prostaglandin E2 and b-fibroblast growth factor which help in production of granulation tissue, angiogenesis and

re-epithelization [19,26]. A recent study [20] on chronic anal fissure also reported 94% healing of fissure at 4 weeks with sucralfate alone although the sample size was small. As such, from our study it can be concluded that sucralfate is clearly beneficial and might play a greater role in future in the treatment of anal fissures as more evidence is generated.

Lastly, although not statistically assessed as a part of our study, as per prevailing prices at the time of the study, metronidazole and sucralfate ointment (Rs 2.5/gram approx.) were far cheaper than comparable amount of 2% diltiazem ointment (Rs 6/gram approx.), and may be a factor worth considering in countries with population belonging to lower ranks of socioeconomic strata.

Limitations of our study include a small sample size and a smaller number of female patients compared to males thus limiting the generalizability in population. Compliance to prescribed regimens are only based on patient self-reporting and cannot be verified. Also, long term recurrence rates were not assessed. Patients of chronic anal fissure were not included in the study and overall efficacy of sucralfate and metronidazole ointment cannot be determined unless these patients are also included.

CONCLUSION

We conclude that, conservative management is quite effective in treating acute fissure in ano, and topical 2% diltiazem is quite effective in this regard. Fixed dose preparations containing topical (7%) sucralfate and (1%) metronidazole is almost as effective as diltiazem and can be considered particularly when allergy or adverse reactions to calcium channel blockers are encountered. It might also be a cheaper alternative to diltiazem, although this requires a statistical cost-benefit analysis. We also recommend further such trials including patients of chronic fissures to generate more definitive evidence on this topic.

Conflict of interests:

The authors report that there is no conflict of interest and no funding was received from any sources for this study. Informed consent was taken from all patients. Study was registered with institutional ethics committee - AIIMSRRP/IEC/2021/703

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Author's contributions:

Conceptualization, MS, RR, TDB.; methodology, MS, RR, TDB, SS software, X.X.; validation, MS, RR, TDB, SS.; formal analysis, MS, RR, TDB.; investigation, MS RR TDB SS.; resources, MS, RR, TDB, SS.; data curation, MS, RR, TDB, SS.; writing—original draft preparation, MS, RR, TDB.; writing—review and editing, MS, RR, TDB.; visualization, MS, RR, TDB, SS.; supervision, MS, RR, TDB, SS.; project administration, MS, RR, TDB, SS
All authors have read and agreed to the published version of the manuscript.

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