

Pregabalin as an Adjunct Analgesic in Multimodal Pain Management in Patients Presenting with Acute Peri-Anal Fissure

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ABSTRACT

Objective: To assess whether Pregabalin has a role as an adjunct analgesic in anal fissures along with standard conservative treatment.

Study Design: Quasi-Experimental Study.

Place and Duration of Study: Sir Ganga Ram Hospital, Lahore Pakistan, from Nov 2021 to Mar 2022.

Methodology: Thirty patients that fulfilled the inclusion criteria presenting to the Outpatient Department of General Surgery were enrolled in the study and assigned to either the standard Treatment-Group or the Pregabalin-Group. Patients were given standard treatment consisting of 0.2% topical GTN cream, stool softeners and analgesics in the form of NSAIDs and Paracetamol for their acute anal fissure, or they were given standard treatment with adjunct Pregabalin 50mg twice a day. The numerical pain score was recorded at enrollment after one week of follow-up.

Results: There was a significant difference between the change in visual analogue scores from baseline between both groups, (p -value of 0.008). There was a significant difference between days till maximum pain relief was achieved between the two groups (p -value of 0.01). 29(96.6%) of fissures were caused due to constipation.

Conclusion Pregabalin provides modest analgesic effects in anal fissures and may be used as an adjunct analgesic in patients with severe pain.

Keywords: Analgesia, Anal fissure, Pregabalin.

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INTRODUCTION

Anal fissures are common in the surgical clinic and cause great discomfort and pain. These linear tears in the anoderm may heal without surgical intervention.¹ However, conservative therapy in the form of topical ointments and adequate analgesia is required. The inciting factor is usually constipation which must also be treated.² A lateral internal sphincterotomy is a gold-standard procedure which may result in faecal incontinence.^{3,4}

Analgesia in Pakistan is a developing modality. Of note is that the abuse of NSAIDs is widespread, with resulting side effects due to a dearth of available analgesics.⁵ Pregabalin attenuates voltage-gated pre-synaptic calcium channels and, by doing so, modulates neuropathic pain. Neuropathic pain also arises from incisions or tears in the epidermis and dermis where nerve fibre disruption occurs, for which Pregabalin can be used.^{6,7} Pregabalin is safe in most patients, with minimal side effects experienced. Serious complications arising from the medication are rarely recorded.⁸

The anoderm in anal fissures is torn; thus, the underlying nerve fibres are exposed; the rationale of this study was that Pregabalin might attenuate the pain experienced from these exposed nerve fibres and provide modest pain relief along with conservative management.^{9,10}

We based the concept of this study on evidence in the literature that shows peri-anal pathology where the skin and dermis are incised, or cut has modest pain modulation and improvement with the use of adjunct Pregabalin. We hypothesized that there would be a significant difference in pain scores at the end of one week for patients taking standard therapy for anal fissures versus those who received standard therapy with Pregabalin.

METHODOLOGY

The quasi-experimental study was conducted Outpatient Clinic of the Department of General Surgery, Sir Ganga Ram Hospital, Lahore Pakistan, from November 2021 to March 2022. Ethical approval was obtained from the Ethical Committee (No:52-Proposal-Publication-FCPS/FJ/ERC.) The sample size was calculated using OpenEpi online sample size calculator using symptomatic fissure healing occurring in 3.2%.⁹

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cases in the first two weeks of treatment and assuming 50% would improve with the addition of Pregabalin.

Inclusion Criteria: Patients of either gender with age ranging from 18-65 presenting with an anal fissure for less than four weeks in the Outpatient Department were included in the study.

Exclusion Criteria: Patients with a history of neuropathic pain such as sciatica, known cases of long-standing proctalgia fugax or patients who were identified on initial examination to have co-existing colorectal pathology such as haemorrhoids that may be causing peri-anal pain besides an anal fissure were excluded from the study.

Follow-up of all patients was done in the Outpatient Department after one week. Thirty patients with acute peri-anal fissures were enrolled by non-probability consecutive sampling technique. All patients received standard medication, i.e. 0.2% GTN cream to apply a pea-sized drop at the anal opening thrice a day, Ispaghul husk one tablespoon morning and evening in warm water, oral diclofenac 50mg one tablet morning and evening, oral Paracetamol 1gram thrice a day and patients identified to have ongoing constipation were given lactulose syrup at bedtime doses adjusted between 15ml and 30ml based on constipation severity. All patients were advised to take Sitz baths in warm water twice daily for 10-15 minutes. Patients enrolled were given either a tablet of Pregabalin 50mg twice a day orally along with standard treatment or standard treatment alone in an alternating fashion.

Patients were asked to complete a questionnaire at enrollment and one-week follow-up. The questionnaire asked for information regarding demographics. Pain scores according to the Visual Analog Score were recorded for all patients on Day one and Day 7. Patients were asked to record which day they received maximum symptomatic relief. After finishing one week of medications, patients were followed up after three days and were asked if their pain had recurred or had increased after termination of treatment.

Data was analyzed using Statistical Package for the social sciences (SPSS) version 24:00. The Shapiro-Wilk test was conducted to determine the normality of data. The visual analogue score on Day 1, visual analogue score on day seven, and change in the visual analogue score had *p*-values <0.05 using the Shapiro-Wilk test; thus, data was not normally distributed. For non-normal data, the difference between the means of the variable was compared using Mann-Whitney U-test. Qualitative variables were compared between the

groups using a chi-square test with the *p*-value ≤0.05 as significant.

RESULTS

In the Standard Treatment-Group, 15 patients were enrolled. The mean age was 33.2±9.75 years. In the Standard Treatment-Group, fissures were caused in 14(93.3%) of participants due to constipation. 2 (13.3%) participants had used lactulose for their constipation prior to enrollment, and 1(6.7%) had used paracetamol for pain relief, and 1(6.7%) had taken an NSAID for pain relief. In the Pregabalin-Group, all patients had fissures caused by constipation. 3(20%) of patients had taken NSAIDs before enrolling in the study for pain relief. The median visual analogue score on day 1 for the Standard Treatment vs. Pregabalin Group was 6(3) and 7(2), respectively, (*p*-value of 0.26). The median for the change in visual analogue score after treatment for Standard Treatment vs. Pregabalin-Group was 3(1) and 5(1), respectively, (*p*-value=0.008) (Table-I). Table-II shows treatment side effects experienced by patients and treatment success and failure characteristics in terms of symptom recurrence or relief. 2(13.3%) of patients in the Standard Treatment-Group experienced retrosternal burning due to NSAIDs. Due to Pregabalin, 4(26.7%) of patients experienced drowsiness. In the Pregabalin-Group, symptomatic relief in days was achieved at a mean number of days of 3.33±0.81 compared to the Standard Treatment-Group, where a mean number of days till symptomatic relief was 4.33±1.04 days (*p*-value of 0.01).

Table-I: Visual Analog Score for both Groups on Day-1 and Day-7 (n=30)

Pain Score	Study Groups		
	Standard Treatment (n=15)	Pregabalin (n=15)	<i>p</i> -value
VAS Day-1 (Median ,Interquartile Range)	6(3)	7(2)	0.26
VAS Day-7 (Median ,Interquartile Range)	3(2)	2(1)	0.32
Change in VAS (Median ,Interquartile Range)	3(1)	5(1)	0.008

Table-II: Maximal Symptomatic Relief in Days Achieved by Patients on Treatment, Pain Recurrence Experienced by Patients and Medication Side Effects Experienced in Both Groups (n=30)

Variables	Study Groups		
	Standard Treatment (n=15)	Pregabalin (n=15)	<i>p</i> -value
Maximal symptomatic relief in days (Mean±S.D)	4.33±1.04	3.33±0.81	0.01
Pain recurrence n(%)	Yes	10(66.7%)	0.14
	No	5(33.3%)	
Retrosternal burning n(%)	2(13.3%)	-	-
Drowsiness n(%)	-	4(26.7%)	-

DISCUSSION

We considered the lower mean pain score clinically significant, as any discomfort, reduction in the clinical setting benefits the patient. The change in visual analogue scores from enrollment was found to have a statistically significant difference ($p=0.008$.) This shows us that Pregabalin did have a modest effect and reduced pain scores more than standard treatment from baseline. Patients further demonstrated that pain relief maximally was achieved on average a day earlier with Pregabalin than with standard treatment alone. This is an important indicator as earlier pain relief translated to earlier patient clinical improvement. The Pregabalin-Group demonstrated lower recurrence of pain scores with a difference of 26%. Though not statistically significant, this holds clinical importance as a lower rate of recurrence or persistence of pain after halting treatment indicates that pain relief was significant.

Pregabalin has been studied as an adjunct analgesic in the post-operative setting, in chronic pelvic pain, prostatitis, proctalgia fugax and intestinal failure where rectal Pregabalin may be used. These studies have shown that Pregabalin helps modulate pain and decreases the intensity experienced.¹¹⁻¹⁴ Similarly, in patients after hemorrhoidectomy where the anoderm is exposed post-operatively, neuropathic pain modulation provided beneficial analgesia, and a nearly three-point mean difference existed in pain scores post-operatively.^{15,16}

Similarly, Pregabalin has been studied in multiple trials as part of pre-emptive analgesia regimens. These are designed to decrease post-operative pain and decrease opioid consumption. Post-operative patients have incisions, similar to an anal fissure where the anoderm has been incised or cut.^{17,18} As an adjunct, Pregabalin plays a role in decreasing the neuropathic pain component. Trials with patients undergoing abdominal surgery, orthopaedic limb surgery, pelvic surgery and anorectal surgery all showed that Pregabalin helped decrease post-operative pain when used in these patients as pre-emptive analgesia.¹⁹⁻²¹ This further strengthens our conclusion that the pain reduction experienced in our patients in the pregabalin-Group was likely due to the reduction of neuropathic pain and thus supported the use of Pregabalin as an adjunct analgesic in anal fissures.

LIMITATION OF STUDY

Our study included a follow-up time of 1 week; comparison at follow-up times up to 8 weeks may give more

information regarding fissure healing rates and if a difference exists. Only one dose of Pregabalin, 100mg per day, was used. Higher doses may be more effective and merit study.

CONCLUSION

Pregabalin provides modest analgesic effects in perianal fissures and may be used as an adjunct analgesic in patients with severe pain.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

VFR & QM: Study design, drafting the manuscript, data interpretation, critical review, approval of the final version to be published.

IW & MSM: Conception, data acquisition, data analysis, drafting the manuscript, approval of the final version to be published.

KI & KJK: Critical review, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated & resolved.

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