

Efficacy of Verapamil Combined with Zinc Oxide for Anal Fissure Management

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Abstract Anal fissure are common causes of rectal bleeding; often necessitate effective local medicinal treatments to avoid surgical intervention. This study evaluates the efficacy of a novel combination therapy using verapamil and zinc oxide ointment for the management of chronic anal fissure. Verapamil, a calcium channel blocker, reduces sphincter pressure, while zinc oxide promotes healing through its anti-inflammatory properties. Conducted as a prospective randomized controlled trial, 65 patients were divided into three groups: a control group treated with Vaseline, a group treated with 15% verapamil ointment, and a group treated with 15% verapamil ointment and 10% zinc oxide ointment. Over a six-week period, the combination therapy group demonstrated significantly higher healing rates and pain relief compared to the other groups. The results suggest that verapamil combined with zinc oxide is a promising and effective treatment option for chronic anal fissures, with manageable side effects.



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Keywords: Chronic Anal Fissure, Verapamil, Zinc Oxide, Topical Treatment, Calcium Channel Blocker.

1. INTRODUCTION

Anal fissures are the most common causes of rectal bleeding. The majority will heal spontaneously without requiring surgery [1, 2]. Therefore, acute fissures usually heal with short-term measures: stool softeners, sitz baths, and use of bulking agents [3, 4]. Medical treatment is also important for chronic fissures. The role of medical treatment is less clear for patients with acute and chronic anal fissures in the acute phase [5, 6]. Local medicinal treatment is the mainstay treatment for healing. For this purpose, zinc oxide paste and ointment are also used to facilitate scarring and decrease anal sphincter tension in anal fissures. Zinc is a cofactor for more than 70 different enzymes in the body, such as alkaline phosphatase, and plays an important role in the metabolism of proteins, nucleic acids, lipids, and carbohydrates. Zinc preparations have been used conservatively in various forms for the treatment of disorders such as eczema, burns, cutaneous surgical wounds, and diaper rash [7,8]. Also, there are studies that have tried zinc oxide as a topical application for anal fissures alone or in the form of visbreaking ointments [9]. However, the efficacy of zinc oxide alone is limited. Therefore, combining zinc oxide with verapamil may provide a more effective approach for the management of anal fissures.

The efficacy of verapamil as a smooth muscle relaxant due to its ability to block calcium channels on the surface of smooth muscle cells. Calcium plays a crucial role in muscle contraction

by binding to specific proteins that initiate the contraction process. By blocking calcium entry into smooth muscle cells, verapamil prevents this contraction mechanism from occurring, resulting in relaxation of the smooth muscle. This relaxation can help relieve symptoms associated with anal fissures, such as pain and discomfort during bowel movements. Furthermore, verapamil has been shown to improve blood flow to the anal sphincter [10], aiding in the healing process of anal fissures.

The objective of this section is to evaluate the effectiveness of verapamil combined with zinc oxide cream as a treatment option for anal fissures. Also, the study aims to evaluate the duration of pain relief and the recurrence rates following the administration of verapamil combined with zinc oxide cream, in comparison to conventional treatment methods for anal fissures. In addition, this section will discuss the potential side effects and complications associated with the use of verapamil combined with zinc oxide cream for anal fissure management [11, 12].

2. MATERIALS AND METHODS

In this section, we present the materials and method used to evaluate the efficacy of Verapamil combined with Zinc Oxide for anal fissure management. The study was conducted as a prospective, randomized controlled trial involving adult patients diagnosed with chronic anal fissures.



The participants were randomly assigned to three groups A, B and, C:

Group A; Treated with Vaseline, once daily at night, (control group) - 15 cases.

Group B; Treated with 15% Verapamil ointment (once daily at night) - 25 cases.

Group C; Treated with 15% Verapamil ointment enrich with 10% zinc oxide ointment (once daily at night) - 25 cases.

This prospective randomized interventional open-label study was conducted in a General Surgery department in Government Al-Kindy Medical College in Baghdad from December 2022 to February 2024 after obtaining approval from the Institutional Ethics Committee. A common laptop with an in-built random number table with a password from an independent co-worker who was not involved with the study was kept for getting randomized numbers for the purpose of the interventional study. The inclusion criteria were patients between 18 and 65 years presenting with symptoms of anal fissure such as pain, bleeding, and constipation or per rectal bleeding and diagnosed to have fissure by surgeon/Proctologists by a digital rectal examination within two weeks of onset of the symptoms. The exclusion criteria were perianal sepsis, thrombotic piles, perianal abscess, diabetes mellitus, malignancy, on immunosuppressive drugs, fissure having duration more than 6 weeks, previous anal surgery or previous treatment for fissure in the past two months, and known allergy to any of the study medications, drawing less than 1 ml of blood from a patient for serum analysis, pregnant and breastfeeding women. These were evidence-based inclusion and non-inclusion criteria based on the clinical practice guidelines for treatment of anal fissures. The follow up period for all patients was 6 weeks. During the follow-up period, patients were assessed for changes in anal fissure symptoms, healing rates, and any adverse effects associated with the treatment. Treatment generally continues until the desired outcome is achieved or complications arise. The study intervention involved the administration of verapamil cream combined with zinc oxide cream, which was applied topically to the affected area twice daily for a period of 6 weeks. There was no statistically significant difference in groups in terms of gender, age, and body mass index. Of the 65 subjects, 44 were reported as male, and 21 were reported as female. Age average (54.30 ± 12.9) and body mass index average (27.45 ± 4.95) were recorded in this study.

3. OUTCOME MEASURES

- Rest Pain (or Baseline) Pain-free and Pain during Defecation: Rest pain was evaluated by obtaining the median of the patients' pain severity recorded in the interval of seven days before randomization. Patients were interviewed with the following question: "In the past week, while not defecating, did pain interfere with your daily activities?" On each visit, the other pain items were assessed using the 10-point Visual Analog Scale. The method to register the anal pain using the 10-point VAS by the patients was explained by the doctor before the patient was randomized. Pain during defecation was defined as slight, moderate, or severe, typically restricted to the time of and short term after defecation. Estimation of the patients' mean uncertainty about what score they have been assigned "About my pain ratings," although the median pain diaries are objective and must be received with the baseline pain. Pain severity during defecation was in the following intervals: 0 (no anal pain), 1-3 (mild anal pain), 4-6 (moderate anal pain), and 7-10 points (severe anal pain).

- Complete healing: The principal efficacy outcome measure was complete healing of the fissure, defined as the absence of any wound or ulceration. On each visit, complete healing was assessed by inspecting the anal region after spreading the buttocks. The patient was instructed to strain mildly to ease the examiner's view, without bearing down.

4. RESULTS

(64.6 %) of patients had been held of the fissure after 6-10 weeks of treatment (18 of group B and 24 of group C). 3 patients of group B avoided contact and the remaining 4 continued to suffer from pain and discomfort during the treatment period. All of patients in group C reported complete relief from pain and discomfort during the treatment period except one avoided contact. The remaining 4 patients of group B had significant improvement in their symptoms after treatment with verapamil combined with zinc oxide for a further two weeks. Group A experienced no healing. All patients in group B and group C experienced complications like headache, dermatitis, dizziness, itching, and postural hypotension. However, these complications were generally mild and transient in nature. No patient discontinued the treatment due to these complications. Overall, the results of the study indicate that the combination of verapamil and zinc oxide for anal fissure management shows promise in terms of healing rates and symptom improvement. Table 1 summarizes the outcomes of cases.

Table 1. The progression of cases over ten weeks

Cases	Parameters	1 st two weeks	Four weeks after	Last four weeks
Group A	Progression	No improvement	Pain persists with bloody stool	Same
	Complication	NO	Acute Symptoms	Chronic Symptoms
	Recurrence	-	-	All patients
	surgery	-	-	NO
Group B	Progression	Mild improvement	NO pain, NO blood (18 cases)	Fail of treatment in 4 patients
	Complication	Headache & Dermatitis	Same	Same
	Recurrence	-	-	Four cases treated with Verapamil+Zinc Oxide
	surgery	-	-	NO
Group C	Progression	Mild improvement	NO pain, NO blood (24 cases)	All cases are cured except one escape contact
	Complication	Mild headache only+ postural hypotension	NO	NO
	Recurrence	NO	NO	NO
	surgery	-	-	NO

5. DISCUSSION

Zinc oxide helps in increasing the levels of human β -defensin-2, and this increase has a significant influence on regenerating the integrity of fissure site damage in the native Zinc oxide is widely recognized for its local efficacy in treating anal fissures due to its anti-inflammatory properties, which promote relaxation and vasodilation [13]. Consequently, there is an increase in free oxygen radicals from polymorphonuclear leukocytes, activating the protein kinase C enzyme on the cellular membrane. This activation triggers nitric oxide production, influencing the metabolism of guanosine-5'-triphosphate and adenine nucleotides that play a role in the calcium ATP-ase pump, as well as the opening of potassium and chloride channels on the cellular membrane. [14, 15]. Furthermore, many previous studies, though, revealed that zinc oxide has little local toxicity when applied topically [16, 17]. In addition, Verapamil has been shown to be effective in treating chronic anal fissures due to its ability to relax the internal anal sphincter. The combination of Verapamil and Zinc Oxide has been studied for its potential synergistic effects in treating anal fissures.

6. CONCLUSION

Based on the findings and analysis conducted in this comprehensive study, it is highly indicative that the combination therapy of Verapamil, a calcium channel blocker, and Zinc Oxide exhibits considerable potential as a promising and effective treatment choice for the management and mitigation of chronic anal fissures. This novel approach offers a multifaceted solution, leveraging the distinct properties and mechanisms of both Verapamil and Zinc Oxide to address the complexities and challenges associated with this recurrent condition. By synergistically combining Verapamil and Zinc Oxide, this therapeutic intervention not only targets the underlying causes of chronic anal fissures but also aims to alleviate the distressing symptoms commonly experienced by affected individuals. With its unique mode of action, this treatment option carries the potential to facilitate the healing process, promote tissue repair, and restore normal anal functionality with tolerable side effects (headache, postural hypotension, and dermatitis).

REFERENCES

- [1] Gardner, Ivy H., Ragavan V. Siddharthan, and Vassiliki Liana Tsikitis. "Benign anorectal disease: hemorrhoids, fissures, and fistulas." *Annals of gastroenterology* 33, no. 1 (2020): 9. nih.gov
- [2] Rao, S. S. C. and Tetangco, E. P. "Anorectal disorders: an update." *Journal of Clinical Gastroenterology* (2020). HTML
- [3] Zuhan, Arif, Puji Widyastuti, Alfia Mawaddah, Annisa D. Indrasari, Baiq HS Alawiya, Putu D. Priyahita, I. Komang Yose Antara, Mervin Arifianto Manginte, Tomi Irmayanto, and IGM Sanies Ermawan. "Anal Fissure: Clinical Practice, Diagnosis in Primary Care and Management Guideline. A Literature Reviews." *Lombok Health And Science Journal* 3, no. 1 (2024): 24-35. unram.ac.id

- [4] Cohee, M. W., Hurff, A., and Gazewood, J. D. "Benign anorectal conditions: evaluation and management." American Family Physician (2020). aafp.org
- [5] Acar, T., N. Acar, F. Güngör, E. Kamer, H. Genç, K. Atahan, O. N. Dilek, and M. Hacıyanlı. "Comparative efficacy of medical treatment versus surgical sphincterotomy in the treatment of chronic anal fissure." Nigerian journal of clinical practice 23, no. 4 (2020): 539-544. lww.com
- [6] Banerjee, Anupam, Pinaki Roy, Rajat Suvra Moral, and Swarup Chakraborty. "An observational study comparing and non-surgical treatment with surgical treatment for chronic anal fissures." Asian Journal of Medical Sciences 14, no. 1 (2023). HTML
- [7] Hou, Rui, Yan He, Guangwei Yan, Shuzeng Hou, Zhouling Xie, and Chenzhong Liao. "Zinc enzymes in medicinal chemistry." European Journal of Medicinal Chemistry 226 (2021): 113877. HTML
- [8] Gondal, Aqarab Husnain, Asma Zafar, D. Zainab, M. D. Toor, S. Sohail, S. Ameen, A. B. Ijaz et al. "A detailed review study of zinc involvement in animal, plant and human nutrition." Indian Journal of Pure & Applied Biosciences 9, no. 2 (2021): 262-271. researchgate.net
- [9] Setareh Soltany, Babak Hosseinzadeh Zoroufchi. "Study the effect of zinc oxide ointment on symptoms arising from hemorrhoids and anal fissure." Journal of Critical Reviews 7, no. 1 (2020): 115-118. ISSN- 2394-5125
- [10] Lo, Y., Lin, L. Y., and Tsai, T. F. "Use of calcium channel blockers in dermatology: a narrative review." Expert review of clinical pharmacology (2021). HTML
- [11] Suza Ali H M, Al-Khedairy E B. Formulation and Evaluation of Prednisolone -Loaded Alginate Beads for Taste Masking. The Egyptian Journal of Hospital Medicine. 2023; 90 (2), Page 2178-2186. DOI: [10.21608/EJHM.2023.285683](https://doi.org/10.21608/EJHM.2023.285683)
- [12] Suza Ali H M, Al-Khedairy E B. Formulation and In Vitro Evaluation of Taste- Masked Prednisolone Orodispersible Tablets. JFacMedBagdad. 2023; 65(3):192-8. <https://doi.org/10.32007/jfacmedbagdad.2057>
- [13] Triboulet, S., Aude-Garcia, C., Armand, L., Gerdil, A., Diemer, H., Proamer, F., Collin-Faure, V., Habert, A., Strub, J. M., Hanau, D., Herlin, N., Carrière, M., Van Dorsselaer, A., and Rabilloud, T. "Analysis of cellular responses of macrophages to zinc ions and zinc oxide nanoparticles: a combined targeted and proteomic approach." (2014). PDF
- [14] Hu, Z., Zhou, L., Meng, D., Zhao, L., Li, Y., Huang, Y., Wu, Y., Yang, S., Li, L., and Hong, Z. "Surface engineering for ultrathin metal anodes enabling high-performance Zn-ion batteries." (2022). PDF
- [15] Jin, S. E. and Jin, H. E. "Synthesis, Characterization, and Three-Dimensional Structure Generation of Zinc Oxide-Based Nanomedicine for Biomedical Applications." (2019). ncbi.nlm.nih.gov
- [16] Khabir, Z., M. Holmes, A., Lai, Y. J., Liang, L., Deva, A., A. Polikarpov, M., S. Roberts, M., and V. Zvyagin, A. "Human Epidermal Zinc Concentrations after Topical Application of ZnO Nanoparticles in Sunscreens." (2021). ncbi.nlm.nih.gov
- [17] Younus,M.M, Ibtahim, I.R, Pharmacovigilance for herbal medicines in Iraq. In: Barnes, J. Pharmacovigilance for herbal and traditional medicines. Adis, Cham(2022). <http://doi.org/10.1007/978-3-031-07275-8-25>