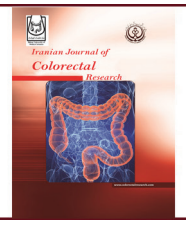
Letter to Editor

Iran J Colorectal Res 2025;13(3):109-110.

Iranian Journal of Colorectal Research



Is L-Arginine Ready for Clinical Use in Chronic Anal Fissure? A Critical Appraisal of the Current Evidence

Semra Demirli Atici*[1*], *MD;* *Aras Emre Canda*[2], *MD;* *Mustafa Cem Terzi*[2], *MD

[1]*Acibadem Kent Hospital, Department of General Surgery, Izmir, Turkey*
[2]*KRC Clinic for Colorectal Surgery and Peritoneal Surface Malignancies, Izmir, Turkey*

Corresponding authors:
Semra Demirli Atici, MD; Acibadem Kent Hospital, Department of General Surgery, 8229/1. Sk. No. 56, Atasehir, Cigli, Izmir 35620, Turkey. **Tel:** +905363624585; **Email:** smrdemirli@hotmail.com

Received: 2025-07-12
Revised: 2025-09-28
Accept: 2025-09-28

Keywords: Fissure in Ano; Arginine; Anal Canal; Nitric Oxide

Please cite this paper as:
Atici SD, Canda AE, Terzi MC. Is L-Arginine Ready for Clinical Use in Chronic Anal Fissure? A Critical Appraisal of the Current Evidence. *Iran J Colorectal Res*. 2025;13(3):109-110. doi: 10.30476/acrr.2026.110366.1281.

Dear Editor

We read the article by Shojaei-Zarghani and Hosseini (1) with interest, in which the authors explore the potential role of L-arginine as a conservative treatment option for chronic anal fissure (CAF). The study examines a biologically plausible yet relatively less well-studied therapeutic approach in a clinical context where non-surgical management is often inadequate and recurrence rates following medical treatment remain common.

The theoretical basis for L-arginine supplementation is supported by existing knowledge; however, clinical evidence remains inconclusive. As a substrate for nitric oxide (NO) synthase, L-arginine can promote relaxation of the internal anal sphincter (IAS) and increase anodermal perfusion (1). Both impaired local blood flow and persistent sphincter hypertonicity are well-known factors contributing to the pathophysiology of CAF and form the mechanistic basis for current pharmacological interventions, including topical nitrates, calcium channel blockers, and botulinum toxin injections (2, 3). In this context, early physiological and pilot clinical studies reporting reductions in resting anal pressure and improvements in anodermal blood flow following topical L-arginine application are particularly noteworthy (4, 5).

However, clinical evidence supporting the use of L-arginine is limited and heterogeneous. A randomized controlled trial cited by the authors suggests that oral L-arginine supplementation may improve fissure healing, reduce pain scores, and decrease anal resting pressure (6). While this study is encouraging, it was limited by a small sample size, a relatively short follow-up period, and the absence of direct comparison with established first-line topical agents such as diltiazem or glyceryl trinitrate. Due to the lack of direct comparative studies and longer follow-up periods, it remains unclear whether L-arginine offers any additional therapeutic benefit beyond established NO-mediated pathways or simply replicates their physiological effects.

Prins et al (7). Reported no significant changes in anal resting pressure or anodermal blood flow following short-term oral L-arginine supplementation in healthy volunteers. The absence of basal sphincter hypertonicity or fissure-related ischemia in this population may partially explain these findings. However, the study highlights

that systemic L-arginine does not consistently produce measurable anorectal physiological effects. Furthermore, evidence suggesting that L-arginine-induced IAS relaxation may occur independently of NO pathways raises additional mechanistic uncertainties, particularly regarding optimal dosing, route of administration, and patient selection (8).

Meta-analyses of CAF treatments report remission rates of approximately 50-70% with topical nitrates and calcium channel blockers; however, significant relapse rates and adverse effect profiles negatively impact treatment adherence (3, 9). Botulinum toxin injections offer higher short-term remission rates but are invasive, costly, and associated with variable long-term durability (10). Lateral internal sphincterotomy remains the most effective treatment in terms of remission, but the well-known risk of fecal incontinence underscores the ongoing need for effective and safe non-surgical alternatives (11). In light of these findings, L-arginine should be considered an adjuvant during the investigational phase and is not yet a competitive alternative.

Furthermore, it is important to highlight the methodological limitations in the existing literature on the use of L-arginine for treating CAF. Current studies on L-arginine are characterized by small sample sizes, heterogeneous study designs, and non-standardized outcome measures. Significant variations exist in the formulation (topical versus oral), dosage, and duration of treatment (12). Pain and quality-of-life assessment tools validated with objective physiological endpoints, such as high-resolution anorectal manometry and laser Doppler flowmetry, are reported inconsistently. Furthermore, CAF is a heterogeneous condition influenced by factors such as constipation severity, pelvic floor dysfunction, and patient-specific comorbidities, which are rarely controlled for in current analyses.

In conclusion, the authors highlight the theoretical and preliminary clinical promise of L-arginine in CAF. Nevertheless, current evidence remains insufficient to support its routine clinical use. Well-designed, adequately powered randomized trials directly comparing topical and oral L-arginine with established pharmacologic agents, incorporating long-term follow-up and standardized physiological and patient-reported outcomes, are essential before its role can be clearly defined. Until such data are available, L-arginine should be regarded as an experimental option rather than a validated component of CAF management.

Authors' Contribution

Demirli Atici S. designed, wrote, and reviewed the manuscript. Canda A.E. and Terzi M.C. reviewed and supervised the work. All authors have read and approved the final version of the manuscript.

Conflict of interest: No conflict of interest.

References

1. Shojaei-Zarghani S, Hosseini SV. Could L-Arginine Be a Feasible Treatment for Chronic Anal Fissure? Iran J Colorectal Res. 2025;13:30-1.
2. Lu Y KM, Lin AY. Diagnosis and Treatment of Anal Fissures in 2021. JAMA 2021;7(325):688-9.
3. Nelson RL TK, Morgan J, Jones A. Non surgical therapy for anal fissure. Cochrane Database Syst Rev 2012;2012(2).
4. Griffin N ZD, Briel JW, Gruss HJ, et al. Topical L-arginine gel lowers resting anal pressure: possible treatment for anal fissure. Dis Colon Rectum. 2002;45(10):1332-6.
5. Gosselink MP DM, Zimmerman DD, Gruss HJ, et al. Treatment of chronic anal fissure by application of L-arginine gel: a phase II study in 15 patients. Dis Colon Rectum. 2005;48(4):832-7.
6. Khalighi Sikaroudi M SM, Shidfar F, Talebi S, Hosseini-Baharanchi FS, et al. L-Arginine is a feasible supplement to heal chronic anal fissure via reducing internal anal sphincter pressure: a randomized clinical trial study. Amino Acids. 2023;55(2):193-202.
7. Prins HA GM, Mitales LE, Buise MP, et al. The effect of oral administration of L-arginine on anal resting pressure and anodermal blood flow in healthy volunteers. Tech Coloproctol. 2005;9(3):229-32;discussion 32-3.
8. Acheson AG GN, Scholefield JH, Wilson VG. L-arginine-induced relaxation of the internal anal sphincter is not mediated by nitric oxide. Br J Surg. 2003;90(9):1155-62.
9. Sierra-Arango F dlH-VJ, Espinosa JP, Moreno-Montoya J, et al. Clinical Outcomes of Medical Management Options for Chronic Anal Fissures in a Long-Term Follow-up: Systematic Review and Meta-Analysis. Dig Dis. 2023;41(5):822-32.
10. Arslan C KE, Altintas T, Pekuz C, et al. Retrospective analysis on the efficacy of botulinum toxin alone versus combined botulinum toxin and topical diltiazem. Int J Colorectal Dis. 2025;40(1)(54).
11. Realis Luc A DVA, Salvatore A, Gravante G, et al. Long-term incontinence rates after traditional lateral internal sphincterotomy: a 5-year retrospective analysis from a high-volume tertiary referral center for proctologic disorders. . Tech Coloproctol. 2025;29(1)(149).
12. Motamed-Gorji N MM, Sikaroudi MK, Agah S, Masoodi N. Exploring the therapeutic potential of L-arginine in chronic anal fissure management: a comprehensive review. Amino Acids. 2025;57(1).