

Critical limb ischemia: Why current options fall short for limb salvage

Written by The Life Science Feed Editorial Team · Published 21 October 2026 · Edited by Mara Voss

Critical limb ischemia (CLI) remains a significant challenge in vascular medicine, with a substantial number of patients progressing to amputation despite current revascularization options. Addressing the underlying impaired angiogenesis and endothelial dysfunction is crucial for improving limb salvage rates, highlighting the urgent need for novel therapies that promote neovascularization and enhance microcirculatory function.

KEY TAKEAWAYS

- **The Pivot:** This preclinical study suggests that combining CD34+ cell therapy with hyperbaric oxygen therapy may synergistically enhance endothelial progenitor cell function, potentially improving limb salvage in critical limb ischemia.
- **The Data:** This preclinical study was conducted in nude mice with induced critical limb ischemia.
- **The Action:** Prescribing clinicians should continue to adhere to current AHA/ACC and SVS guidelines for CLI management, as this investigational approach requires further human clinical trials before integration into routine practice.

Background

Critical limb ischemia (CLI) represents a significant unmet clinical need. Despite advances in surgical and endovascular revascularization, a substantial proportion of patients progress to amputation. The underlying pathophysiology involves impaired angiogenesis and endothelial dysfunction, hindering tissue repair and perfusion. Novel therapies that can promote neovascularization and improve microcirculatory function are desperately needed.

Study Details

This study investigated the effects of combining CD34+ cell therapy and hyperbaric oxygen therapy (HBOT) on endothelial progenitor cells (EPCs) derived from patients with peripheral artery occlusive disease (PAOD).⁵ The central hypothesis was that HBOT could enhance the regenerative capacity of CD34+ cells, leading to improved limb salvage.⁵ The researchers isolated EPCs from PAOD patients before and after CD34+ cell therapy combined with HBOT.⁵ These "rejuvenated" EPCs were then transplanted into nude mice with induced critical limb ischemia.⁵ The primary outcome was limb salvage, assessed by measuring blood perfusion and monitoring ulcer healing.

Potential Mechanism

The study suggests that HBOT may enhance EPC function by increasing the expression of pro-angiogenic factors and reducing oxidative stress. CD34+ cells, a subset of hematopoietic stem cells, are known to promote neovascularization and tissue repair.^{6,7} The combination of these two therapies appears to create a synergistic effect, leading to more robust

angiogenesis and improved limb perfusion.⁴ Is this a durable effect, or merely a transient benefit? Further investigation into the long-term effects is warranted.

Comparison to Guidelines

Current guidelines from the American Heart Association (AHA) and the Society for Vascular Surgery (SVS) emphasize risk factor modification, antiplatelet therapy, and revascularization strategies for patients with CLI. While cell therapy is mentioned as a potential investigational approach, it is not yet a standard of care. The AHA/ACC guidelines on peripheral artery disease acknowledge the potential of regenerative medicine approaches but emphasize the need for further research to establish efficacy and safety. This preclinical study, while promising, does not yet warrant a change in clinical practice. It does, however, provide a rationale for further investigation into the combined use of CD34+ cell therapy and HBOT.

Study Limitations

This study has several limitations. First, it is a preclinical study conducted in nude mice, which may not accurately reflect the complex pathophysiology of CLI in humans. Second, the sample size was small, limiting the statistical power of the findings. Third, the study did not include a control group treated with CD34+ cell therapy alone, making it difficult to determine the independent contribution of HBOT. We also need to be skeptical about reproducibility. Was this experiment meticulously repeated, or a one-off fluke? Transparency in methods is paramount.

Conclusion

The results of this preclinical study suggest that combining CD34+ cell therapy and hyperbaric oxygen therapy may enhance the regenerative capacity of EPCs and improve limb salvage in critical limb ischemia.⁴ While these findings are promising, further research is needed to confirm these results in human clinical trials. We need larger, randomized, controlled trials to determine the efficacy and safety of this combined therapeutic approach before it can be considered for routine clinical use.

Further, the optimal dosing and duration of HBOT, as well as the ideal timing and frequency of CD34+ cell administration, remain to be elucidated. The long-term safety of repeated HBOT and cell therapy also requires rigorous evaluation, particularly concerning potential risks such as oxidative damage or tumorigenicity. Future research should also explore the specific mechanisms by which HBOT enhances CD34+ cell function at a molecular level, potentially identifying novel therapeutic targets.

The economic implications of this combined therapy also warrant consideration. Both CD34+ cell therapy and HBOT are resource-intensive interventions. A comprehensive cost-effectiveness analysis will be crucial to determine the feasibility of widespread adoption, even if clinical efficacy is established. This would involve comparing the costs of the combined therapy against the long-term costs associated with amputation and chronic wound care, which are substantial for CLI patients.

In conclusion, while this preclinical study offers a compelling rationale for further investigation into the synergistic potential of CD34+ cell therapy and HBOT for critical limb ischemia, the journey from bench to bedside is long. Robust, well-designed human clinical trials are the indispensable next step to validate these promising findings and ultimately

translate them into a meaningful improvement in limb salvage rates and quality of life for patients suffering from this debilitating condition.

CLINICAL IMPLICATIONS

The most striking consequence of this preclinical study is the potential for a paradigm shift in critical limb ischemia (CLI) management. Current guidelines from the American Heart Association (AHA) and the Society for Vascular Surgery (SVS) focus on revascularization and risk factor modification. This research, while early, points towards a future where regenerative medicine, specifically combined CD34+ cell therapy and hyperbaric oxygen therapy (HBOT), could become a viable limb salvage strategy. This is a significant leap beyond current investigational approaches.

For clinicians, this means keeping an eye on forthcoming human trials. The evidence is thin for now, limited to preclinical mouse models. We need robust, randomized controlled trials to establish efficacy and safety in patients. Industry players like biotech firms developing cell therapies and medical device companies specializing in HBOT should recognize the potential synergy. Investment in larger clinical studies is crucial to move this from a promising concept to a tangible treatment option.

Patients with CLI currently face devastating outcomes, including amputation, when conventional treatments fail. This combined therapy offers a glimmer of hope for improved limb salvage and quality of life. However, it is vital to manage expectations. This is investigational. It is not yet a standard of care. The long-term safety of repeated HBOT and cell therapy, including potential risks like oxidative damage or tumorigenicity, still requires rigorous evaluation.

Future research must clarify optimal dosing, duration, and timing for both components of this combined therapy. We also need to understand the precise molecular mechanisms by which HBOT enhances CD34+ cell function. This could unlock further therapeutic targets. This study provides a strong rationale for continued investigation, but it does not yet warrant a change in clinical practice.

EDITORIAL & AI STANDARDS

AI tools are used to structure and summarise evidence from peer-reviewed primary sources. Articles that carry a signed Editor's take have been read in full by William Lopes. The others are not individually read by an editor, so check the cited source before relying on a figure.

REFERENCES

1. Conte, M. S., Bradbury, A. W., Creager, M. A., et al. (2019). Global vascular guidelines on the management of chronic limb-threatening ischemia. *European Journal of Vascular and Endovascular Surgery*, 58(1), 1-81.e33.
2. Gerhard-Herman, M. D., Gornik, H. L., Barrett, C., et al. (2016). 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, 69(11), e71-e126.
3. Mills, J. L., Sr., Conte, M. S., Armstrong, D. G., et al. (2014). The Society for Vascular Surgery Lower Extremity Threatened Limb Classification System: Improving Uniformity in Clinical Approach and Reporting. *Journal of Vascular Surgery*, 59(1), 258-266.

4. 4. Hsu SL, Yin TC, Shao PL, et al. Hyperbaric oxygen facilitates the effect of endothelial progenitor cell therapy on improving outcome of rat critical limb ischemia. *Am J Transl Res*. 2019;11(4):1948-1964. PMID:31105810
5. 5. Chen YC, Sheu JJ, Chiang JY, et al. Circulatory Rejuvenated EPCs Derived from PAOD Patients Treated by CD34(+) Cells and Hyperbaric Oxygen Therapy Salvaged the Nude Mouse Limb against Critical Ischemia. *Int J Mol Sci*. 2020;21(21). doi:10.3390/ijms21217887
6. 6. Sietsema WK, Kawamoto A, Takagi H, Losordo DW. Autologous CD34+ Cell Therapy for Ischemic Tissue Repair. *Circ J*. 2019;83(7):1422-1430. doi:10.1253/circj.CJ-19-0240
7. 7. Tournais C, Pignon B, Sevestre MA, et al. Cell therapy in critical limb ischemia: A comprehensive analysis of two cell therapy products. *Cytotherapy*. 2017;19(2):299-310. doi:10.1016/j.jcyt.2016.10.013

LICENCE & RIGHTS

© 2026 The Life Science Feed. All rights reserved. This content is produced for medical education purposes. It may not be reproduced, distributed, or transmitted without prior written permission from The Life Science Feed.

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com