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Levosimendan in burn wound ischemia: Mechanistic rationale and therapeutic potential

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To Editor,

Burn injuries frequently result in progressive tissue ischemia driven by microvascular dysfunction, oxidative stress, and inflammatory cascades, which impair tissue viability and delay healing. The zone of stasis—initially viable but vulnerable tissue surrounding the necrotic core—represents a key therapeutic target, as its progression to irreversible necrosis markedly worsens outcomes.^{1,2} Despite advances in burn care, pharmacologic agents specifically designed to preserve microvascular perfusion and cellular integrity in this region remain limited.

Levosimendan, a calcium sensitizer and ATP-sensitive potassium (KATP) channel opener with an established role in acute heart failure, exerts cytoprotective effects beyond its inotropic actions.³ These include vasodilation, mitochondrial stabilization, reduction of oxidative stress markers (e.g., malondialdehyde, nitric oxide), restoration of antioxidant enzyme activity (e.g., superoxide dismutase), and modulation of inflammatory pathways (e.g., improved IL-10/IL-6 ratio, reduced TNF- α and IL-6).³⁻⁷ Experimental studies have shown levosimendan mitigates ischemia-reperfusion (I/R) injury in heart, lung, kidney, intestine, and brain, improving tissue oxygenation, endothelial function, and cellular resilience under ischemic conditions.⁵⁻¹⁰

These mechanisms align with the core drivers of burn zone-of-stasis progression: reactive oxygen species accumulation, endothelial dysfunction, pro-inflammatory cytokine release, and impaired regional perfusion.^{1,2} In non-burn ischemic and inflammatory models, levosimendan has reduced oxidative damage, preserved tissue viability, and enhanced perfusion without increasing oxygen demand.⁶⁻¹³ While these findings provide mechanistic plausibility, "However, no data exist

on levosimendan in burn models or patients, precluding direct extrapolation due to burn-specific pathophysiology and altered pharmacokinetics.

Levosimendan is an inodilator with systemic vasodilatory effects, raising theoretical concern in early burn shock where vasopressor support (e.g., norepinephrine) is often required to maintain systemic perfusion.^{1,2} However, clinical evidence from septic shock and cardiogenic shock demonstrates that levosimendan can be safely combined with vasopressors when needed, with adjustments to maintain blood pressure and without excessive vasopressor escalation.^{3,14,15} Moreover, levosimendan improves microvascular perfusion and tissue oxygenation in ways that extend beyond pure systemic vasodilation, potentially relevant to regional ischemia in burns.^{4,7} The net hemodynamic impact in burn-specific settings remains unknown and requires dedicated evaluation.

The safety profile of systemic levosimendan is well-characterized, with predictable, dose-dependent hemodynamic effects.^{3,4} Burn injury introduces complex changes in vascular permeability, inflammation, and drug distribution that could influence response. Previous pharmacologic approaches to burn ischemia have shown mechanistic promise but limited clinical translation, emphasizing the need for rigorous, burn-specific investigation. For example, nicorandil (another KATP channel opener) reduced burn wound progression and increased tissue survival in the zone of stasis by enhancing skin blood flow and attenuating ischemia-reperfusion injury in a rat comb burn model.¹⁶

In summary, levosimendan's pharmacologic profile—microvascular modulation, mitochondrial protection, and anti-inflammatory effects—offers conceptual

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Study Highlights

- Burn zone of stasis progresses due to microvascular dysfunction, oxidative stress, and inflammation.
- Salvage of zone of stasis remains challenging despite advances in burn care.
- Levosimendan protects against ischemia-reperfusion injury in multiple organs via KATP opening, vasodilation, antioxidant, and anti-inflammatory effects.
- KATP openers (e.g., nicorandil) reduce burn wound progression in preclinical models.
- Suggests levosimendan repurposing for burn wound ischemia based on mechanistic overlap.
- Emphasizes plausibility from non-burn models while stressing absence of burn-specific data.
- Proposes preclinical burn studies to assess zone of stasis salvage.
- Highlights need for rigorous evaluation given burn-unique pathophysiology and safety considerations.

relevance to burn-associated tissue ischemia. Its efficacy and safety in this context are unproven, but the available evidence justifies hypothesis-driven preclinical studies in established burn models to assess effects on zone-of-stasis salvage, perfusion, oxidative stress, and histology.

Competing Interests

The author declare that they have no conflict of interest.

Declaration of AI-assisted Tools in the Writing Procedure

This manuscript was prepared and edited exclusively by the author; artificial intelligence was used only to correct the language.

Ethical Approval

Not applicable.

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References

1. Palackic A, Jay JW, Duggan RP, Branski LK, Wolf SE, Ansari N, et al. Therapeutic strategies to reduce burn wound conversion. *Medicina (Kaunas)* **2022**; 58: 922. doi:10.3390/medicina58070922
2. Rowan MP, Cancio LC, Elster EA, Burmeister DM, Rose LF, Natesan S, et al. Burn wound healing and treatment: review and advancements. *Crit Care* **2015**; 19: 243. doi:10.1186/s13054-015-0961-2
3. Papp Z, Agostoni P, Alvarez J, Bettex D, Bouchez S, Brito D, et al. Levosimendan efficacy and safety: 20 years of SIMDAX in clinical use. *J Cardiovasc Pharmacol* **2020**; 76: 4-22. doi:10.1097/fjc.0000000000000859
4. Morelli A, Donati A, Ertmer C, Rehberg S, Lange M, Orecchioni A, et al. Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. *Crit Care* **2010**; 14: R232. doi:10.1186/cc9387
5. Shi F, Bao H, Meng F, Pang Y. Levosimendan alleviates myocardial ischemia-reperfusion injury by regulating mitochondrial autophagy through cGAS-STING signaling pathway. *J Clin Biochem Nutr* **2025**; 77: 74-8. doi:10.3164/jcbn.25-8
6. Grossini E, Molinari C, Pollesello P, Bellomo G, Valente G, Mary D, et al. Levosimendan protection against kidney ischemia/reperfusion injuries in anesthetized pigs. *J Pharmacol Exp Ther* **2012**; 342: 376-88. doi:10.1124/jpet.112.193961
7. García-Bardon A, Kamuf J, Ziebart A, Liu T, Krebs N, Dinges B, et al. Levosimendan increases brain tissue oxygen levels after cardiopulmonary resuscitation independent of cardiac function and cerebral perfusion. *Sci Rep* **2021**; 11: 14220. doi:10.1038/s41598-021-93621-x
8. Sezen Ş C, Kucuk A, Özer A, Kılıç Y, Mardin B, Alkan M, et al. Assessment of the effects of levosimendan and thymoquinone on lung injury after myocardial ischemia reperfusion in rats. *Drug Des Devel Ther* **2018**; 12: 1347-52. doi:10.2147/dddt.S160092
9. Aygun H, Olguner C, Koca U, Ergur BU, Sisman AR, Isguven D, et al. The effect of post-reperfusion levosimendan in an experimental intestinal ischemia-reperfusion model. *J Anesth Analg Crit Care* **2022**; 2: 45. doi:10.1186/s44158-022-00074-3
10. Karakus E, Halici Z, Albayrak A, Bayir Y, Aydin A, Unal D, et al. Beneficial pharmacological effects of levosimendan on antioxidant status of acute inflammation induced in paw of rat: involvement in inflammatory mediators. *Basic Clin Pharmacol Toxicol* **2013**; 112: 156-63. doi:10.1111/bcpt.12004
11. Krychtiuk KA, Watzke L, Kaun C, Buchberger E, Hofer-Warbinek R, Demyanets S, et al. Levosimendan exerts anti-inflammatory effects on cardiac myocytes and endothelial cells in vitro. *Thromb Haemost* **2015**; 113: 350-62. doi:10.1160/th14-06-0549
12. Fadilah NIM, Phang SJ, Kamaruzaman N, Salleh A, Zawani M, Sanyal A, et al. Antioxidant biomaterials in cutaneous wound healing and tissue regeneration: a critical review. *Antioxidants (Basel)* **2023**; 12: 787. doi:10.3390/antiox12040787
13. Comino-Sanz IM, López-Franco MD, Castro B, Pancorbo-Hidalgo PL. The role of antioxidants on wound healing: a review of the current evidence. *J Clin Med* **2021**; 10: 3558. doi:10.3390/jcm10163558
14. Gordon AC, Perkins GD, Singer M, McAuley DF, Orme RM, Santhakumaran S, et al. Levosimendan for the prevention of acute organ dysfunction in sepsis. *N Engl J Med* **2016**; 375: 1638-48. doi:10.1056/NEJMoa1609409
15. Susilo H, Aldian FM, Wungu CDK, Alsagaff MY, Sutanto H, Multazam C. Levosimendan, a promising pharmacotherapy in cardiogenic shock: a comprehensive review. *Eur Cardiol* **2024**; 19: e21. doi:10.15420/ecr.2024.16
16. Choi J, Kim R, Kim J, Jeong W, Park SW, Lee HW, et al. Nicorandil reduces burn wound progression by enhancing skin blood flow. *J Plast Reconstr Aesthet Surg* **2018**; 71: 1196-206. doi:10.1016/j.bjps.2018.03.020