Nazari Taloki, *BioImpacts.* 2026;16:33590
doi:10.34172/bi.33590

Article Info

Article Type:
Letter to the Editor

Article History:
Received: 22 Feb. 2026
Revised: 26 Apr. 2026
Accepted: 6 May 2026
ePublished: 25 May 2026

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.

Funding
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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