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Potential of pentoxifylline in preventing reperfusion injury after surgery on limb ischemia: a literature review

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ARTICLE INFO

Article history:
Submitted: 30. 12. 2024
Revised: 2. 2. 2025
Accepted: 28. 2. 2025
Available online: 27. 10. 2025

Klíčová slova:
Akutní ischemie končetin
Antioxidant
Ischemie končetin
Pentoxifylin
Reperfuzní poškození

SOUHRN

Kontext: Pro akutní ischemii končetin (acute limb ischemia, ALI) je charakteristická náhlá ztráta průtoku krve v dolních končetinách v důsledku embolie nebo trombózy. Léčba ALI je nesmírně důležitá, protože popsaný stav může vést k těžkým komplikacím včetně ischemicko-reperfuzního poškození (IRI) během revaskularizačního výkonu. Při IRI dochází ke složitým funkčním a strukturálním změnám po obnově průtoku krve, vedoucím k rozvoji zánětu a k oxidačnímu stresu. Tyto patologické procesy mohou zhoršit poškození tkání a bránit zotavení. Ukázalo se, že pentoxifylin by mohl dobře sloužit jako potenciální lék díky jeho schopnosti zlepšit průtok krve a snížit zánětlivou odpověď.
Cíl: Tento přehled literatury se zabývá úlohou pentoxifylinu (PTX) při zmírňování ischemicko-reperfuzního poškození spojeného s akutní ischemií končetin jako stavu významně ztěžujícího stanovení prognózy a zhoršujícího přežití.
Metody: Tento přehled je syntézou poznatků z četných preklinických a klinických studií zkoumajících ochranné účinky PTX v různých modelech IRI. Mezi primární mechanismy účinku patří inhibice tvorby faktoru aktivujícího krevní destičky (platelet-activating factor, PAF), tlumení zánětu a zlepšování hemoreologických parametrů, které dohromady posilují mikrocirkulaci během reperfuze.
Výsledky: Pomocí modelů ischemie kosterního svalu a mozku se prokázalo se, že PTX účinně omezuje nekrózu tkání a zlepšuje výsledný stav. Navíc se ukázalo, že PTX omezuje poškození plic v důsledku IRI. Tento přehled rovněž vyzdvihuje potenciální přínos kombinační léčby, zvláště ve spojení s antioxidancii jako vitaminem C, která může dále posílit ochranné účinky PTX.
Závěry: Pentoxifylin tak představuje slibný lék pro prevenci reperfuzního poškození po ischemických příhodách, jako je ALI. Nicméně – aby bylo možno optimalizovat jeho využití a potvrdit jeho účinnost u různých lidských populací – je zapotřebí dalších klinických studií.

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Keywords:
Acute limb ischemia
Antioxidant
Limb ischemia
Pentoxifylline
Reperfusion injury

ABSTRACT

Background: Acute limb ischemia (ALI) is characterized by a sudden loss of blood flow to the lower limbs, often resulting from embolism or thrombosis. Management of ALI is critical, as it can lead to severe complications, including ischemia-reperfusion injury (IRI) during revascularization procedures. IRI involves complex functional and structural changes following restoration of blood flow, leading to inflammation and oxidative stress. These pathological processes can exacerbate tissue damage and impede recovery. Pentoxifylline has emerged as a potential therapeutic agent due to its ability to improve blood flow and reduce the inflammatory response.
Aim: This literature review investigates the role of pentoxifylline (PTX) in reducing ischemia-reperfusion injury associated with acute limb ischemia (ALI), a condition that poses significant challenges to prognosis and survival.
Methods: This review synthesizes findings from multiple preclinical and clinical studies examining the protective effects of PTX across different models of IRI. The primary mechanisms of action include inhibition of platelet-activating factor (PAF) production, reduction of inflammation, and enhancement of hemorheological properties, which collectively improve microcirculation during reperfusion.
Results: PTX has demonstrated efficacy in reducing tissue necrosis and improving outcomes in models of skeletal muscle and cerebral ischemia. In addition, it has been shown to reduce lung damage from IRI. This review also highlights the potential benefits of combination therapy, particularly with antioxidants such as vitamin C, which may further enhance the protective effects of PTX.
Conclusions: Pentoxifylline shows promise as a therapeutic agent to prevent reperfusion injury after ischemic events such as ALI. However, further clinical trials are needed to optimize its application and confirm its efficacy in human populations.

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DOI: 10.33678/cor.2025.032

Please cite this article as: Johan ARD, Limanto DH, Soebroto H. Potential of pentoxifylline in preventing reperfusion injury after surgery on limb ischemia: a literature review. Cor Vasa 2025;67:646–650.

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Introduction

Acute limb ischemia (ALI) is a lower extremity ischemia that occurs suddenly and has a poor prognosis, not only in the extremities but also in survival. According to research in the UK, the incidence of embolism, thrombosis due to occlusive atherosclerotic lesions, and stent or graft-related thrombosis is quite high.[1] Speed and accuracy in establishing and managing are the keys to successful ALI management. ALI can be classified based on clinical findings and Doppler ultrasound results from related blood vessels. Management can be given according to the ALI classification, ranging from heparinization, revascularization with thrombolytic agents, endovascular management, and surgery to amputation. In revascularization management, side effects are not uncommon, namely vascular reperfusion injury, also known as ischemia-reperfusion injury (IRI).

IRI is a term used to describe functional and structural changes that appear during the recovery of blood flow after a period of ischemia. This may occur as a result of a vicious cycle of vascular, endothelial and mitochondrial dysfunction, with reduced local perfusion, intense dysfunctional changes, edema and many other implications leading to the release of proinflammatory cytokines and free radicals.[2,3] This occurs after ischemic tissue is reperfused, the influx of molecular oxygen catalyzes xanthine oxidase to degrade hypoxanthine to uric acid and thereby release the highly reactive superoxide anion (O^{2-}). The main consequence of hydroxyl radical production is peroxidation of the lipid structure of the cell membrane resulting in the production and release of systemic proinflammatory eicosanoids, impaired cell permeability and ultimately cell death.[3] Pentoxifylline (PTX), a nonspecific phosphodiesterase derivative of xanthine, has emerged as a promising agent that can attenuate the inflammatory response through several mechanisms.[4] This drug improves blood flow by reducing viscosity and enhancing red blood cell flexibility.[5] Pentoxifylline, a non-selective phosphodiesterase inhibitor, has been extensively studied for its potential to mitigate reperfusion injury following ischemic events. This literature review synthesizes findings from various studies focusing on the effects of pentoxifylline in different models of IRI.

Acute limb ischemia

Acute limb ischemia (ALI) is a rapid reduction in lower limb blood flow due to acute occlusion of a peripheral artery that can result in amputation, regardless of the underlying cause unless appropriate treatment is provided.[1] Acute limb ischemia occurs as a result of an acute (<2 weeks) reduction in blood supply.[6,7] ALI is a vascular emergency and requires rapid revascularization with an endovascular, surgical, or hybrid approach to avoid limb loss. Sudden ischemia affects all the metabolically active tissues of the limb including skin, muscles, and nerves.

ALI is most commonly caused by arterial thrombosis due to plaque development and complications which account for 40% of total events, followed by arterial embolism (30%), graft thrombosis (20%), popliteal aneurysm thrombosis (5%) and trauma (5%).[8]

The classic term for ALI patients is known as the "6 Ps": pain, pallor, paralysis, pulse deficit, paresthesia and poikilothermia are important keywords for detecting ALI.[9] Steps for emergency diagnosis are described, emphasizing the role of clinical and imaging data, especially duplex ultrasonography, CT angiography, and digital subtraction angiography. Rutherford criteria are used to assess the severity of ALI (**Table 1**).

A wide range of therapeutic techniques ranging from pharmacological thrombolysis to interventional techniques to surgical revascularization and minor or major amputation if necessary.[8] After the diagnosis of ALI, intravenous injection of unfractionated heparin (50–100 units/kg) is given immediately to prevent the development of secondary thrombosis if heparin is not contraindicated. ALI with a severity classification of III is irreversible ischemia and requires amputation. Patients with extensive ischemia due to high occlusion and when time has passed since onset, have a high risk of severe ischemia-reperfusion injury; thus, amputation of the limb may be necessary to prioritize the patient's life.[1]

Reperfusion injury

Ischemia-reperfusion injury is an event where reperfusion can worsen cell damage that has been caused by ischemia. Some of the most common pathologies that result in ischemia are sepsis, cerebral infarction, acute coronary syndrome, organ transplantation, and limb injury. A sudden increase in blood and oxygen flow after revascularization can trigger activation of the inflammatory process, release of cytokines, and result in further damage to cells and their membranes. The organs usually involved in vascular reperfusion injury are the heart, brain, liver,

Table 1 – Stages of acute limb ischemia based on Rutherford classification[10]

Stage	Prognosis	Findings		Doppler signal	
		Sensory loss	Muscle weakness	Arterial	Venous
I	Limb viable, not immediately threatened	None	None	Audible	Audible
IIa	Limb marginally threatened, salvageable if promptly treated	Minimal (toes)	None	Often inaudible	Audible
IIb	Limb immediately threatened, salvageable with immediate revascularization	More than toes, pain at rest	Mild or moderate	Inaudible	Audible
III	Limb irreversibly damaged, major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Paralysis (rigor)	Inaudible	Inaudible

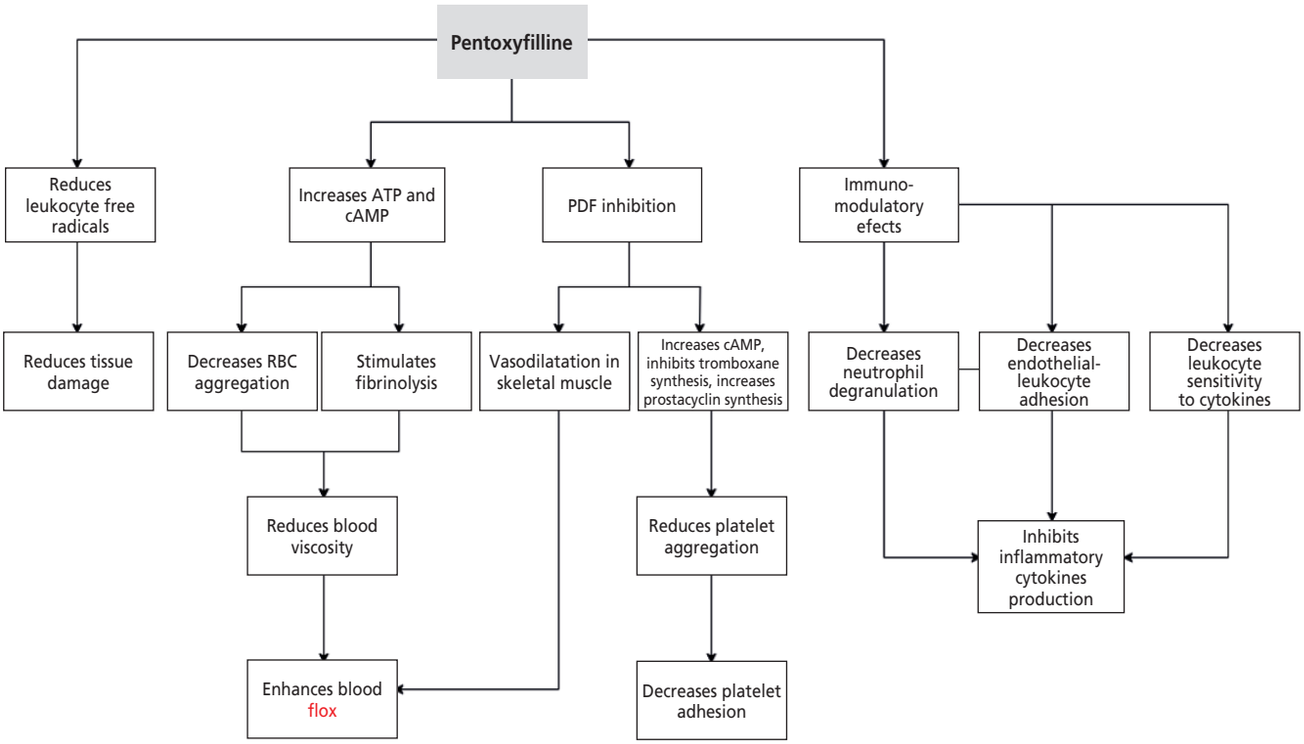

Fig. 1 – Pentoxyfilline pathway to prevent reperfusion injury.

skeletal muscle, intestines and kidneys, leading to systemic inflammation, ending in multiorgan failure.[11] In some cases after revascularization, the phenomenon of "second hit" where greater damage occurs to cells and membranes that have been damaged often occurs. Early revascularization must be performed to prevent reperfusion injury.

Injury mechanisms involved in vascular reperfusion a include increased generation of reactive oxygen species, vasoconstriction of microvasculature, adhesion and activation of neutrophils to the endothelial layer, and release of cytokines. Ischemia results in a lack of oxygen, glucose, and other substances needed for metabolism resulting in anaerobic mitochondrial glycolysis which produces two molecules of adenosine triphosphate (ATP) and lactic acid, which results in a decrease in tissue pH, which then acts through negative feedback to inhibit further ATP production. Ischemia induces the expression of a large number of genes, which play a role in the tissue response to ischemic damage including activating several genes, in particular transcription factors, including activating protein-1 (AP-1), hypoxia-inducible factor-1 (HIF-1) and nuclear factor-kappa B (NF-κB).[3]

IRI induce the expression of various cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) and platelet-activating factor (PAF). TNF-α is a potent chemoattractant and early response cytokine produced by activated macrophages, monocytes, T lymphocytes, natural killer cells and fibroblasts that then induces the expression of IL-1, IL-6, IL-8, and PAF. Several studies in animal models have demonstrated the potential of TNF-α blockade as a therapeutic modality to reduce the severity of IRI.[3]

Xanthine oxidase shows different distribution and susceptibility to oxidant-mediated IRI. Inhibition of xanthine oxidase activity, prior to ischemia, reduces superoxide production and thereby reduces the severity of reperfusion injury in animal models. Results in humans are also promising.[3]

Pentoxifylline

Pentoxifylline is a methylxanthine derivative and phosphodiesterase inhibitor (PDEi) with potent hemorheological properties. Pentoxifylline therapy produces various physiological changes at the cellular level. Pentoxifylline acts as an immunomodulator by increasing leukocyte deformability and chemotaxis, reducing leukocyte endothelial adhesion, reducing neutrophil degranulation and superoxide release, reducing the production of monocyte-derived tumor necrosis factor, reducing leukocyte response to interleukin 1 and tumor necrosis factor, inhibiting the activation of T and B lymphocytes, and reduces natural killer cell activity.[12] Pentoxifylline exerts its protective effects through several mechanisms as shown in **Figure 1**:

1. **Inhibition of platelet-activating factor (PAF):** Studies have demonstrated that pentoxifylline can significantly reduce the levels of PAF, a key mediator in inflammatory responses during reperfusion. For instance, in a canine model of skeletal muscle ischemia-reperfusion, administration of pentoxifylline prior to reperfusion resulted in decreased PAF levels and reduced muscle necrosis.[5] Similarly, research involving rabbits indicated that pentoxifylline treat-

ment led to a significant decrease in PAF levels after reperfusion compared to control groups.[4]

2. **Anti-inflammatory effects:** Pentoxifylline has been shown to attenuate inflammation by inhibiting neutrophil activation and adhesion, which are critical processes in the pathophysiology of reperfusion injury, resulting in reduced neutrophil degranulation, decreased leukocyte adhesion to endothelial cells, and diminished leukocyte responsiveness to cytokines.[5] In a rat model of cerebral IRI, pentoxifylline treatment was associated with reduced neurological deficits and improved neuronal survival, suggesting its role in modulating inflammatory pathways.[13]
3. **Improvement of hemorheological properties:** The drug enhances the deformability of red blood cells and reduces blood viscosity, which can improve microcirculation during reperfusion.[13,14] It also increases red blood cell flexibility by increasing erythrocyte ATP and cyclic nucleotide levels.[5] This is particularly important as impaired blood flow can exacerbate tissue damage.
4. Pentoxifylline induces vasodilation in the blood vessels of skeletal muscles by inhibiting phosphodiesterase (PDE) and raising cAMP levels.[5]
5. Pentoxifylline suppresses the production of leukocyte-derived free radicals during peripheral ischemia in patients with peripheral vascular disease. This helps maintain the filterability of unfractionated leukocytes, reducing tissue damage caused by ischemia.[15]

The medication may enhance tissue perfusion in these patients by improving blood circulation and reducing signs and symptoms of ischemic pain. However, while it can provide symptom relief, it is not intended to replace standard treatments for peripheral vascular disease.[5]

Pentoxyphilline and reperfusion injury

Ischemia-reperfusion (IR) is understood as a complicated series of events that involve interactions among the vascular endothelium, interstitial spaces, circulating cells, and various biochemical components that occur after ischemia. Inflammation plays a crucial role in IR, and the participation of the innate immune system. Ischemia-reperfusion (IR) begins with an episode where blood supply is restricted to an organ, leading to cell death. The return of blood flow exacerbates the damage. Ischemia causes tissue hypoxia, resulting in the accumulation of metabolic intermediates and reactive oxygen species (ROS) such as superoxide, hydrogen peroxide, and hydroxyl radicals. These ROS increase intracellular calcium levels, alter pH, and deplete ATP and nitric oxide (NO), ultimately damaging cell organelles and causing necrotic cell death.[16] That mechanism leads to ischemia-reperfusion injury (IRI).

Influx of activated neutrophils plays a key role in the mediation of IRI.[16] Not surprisingly, pentoxifylline treatment has been reported to lessen such damage in numerous rodent studies, including studies focusing on the heart or brain. From the mechanism of action above, pentoxifylline used because it suppresses production of leukocyte-derived free radicals during peripheral ischemia. Pentoxifylline prevents neutrophil interaction with endothelium and prevents leukocyte degranulation. This will reduce endothelial damage.[17] PDE inhibition by pentoxifylline may reduce the inflammatory response and ischemia-reperfusion damage after lower limb ischemia and reperfusion.[18]

In rabbit models of acute limb ischemia, pentoxifylline was shown to attenuate PAF production during reperfusion. The study reported a significant decrease in PAF levels post-treatment, indicating that PTX may effectively mitigate inflammatory responses associated with limb reperfusion injury.[4] Another study found that administration of PTX at high doses decreased the rate of skeletal muscle necrosis. PTX at a dose of 25 mg/kg immediately before reperfusion decreased the rate of muscle necrosis and PAF levels in venous effluent from isolated gracilis dogs.[19] Endothelial damage following ischemia and reperfusion is marked by increased permeability, cell swelling, and impaired vasorelaxation in response to acetylcholine. In a rabbit hindlimb ischemia model, endothelial cell-dependent vasorelaxation was maintained with intra-arterial administration of PTX during reperfusion, unlike in the control group. The variation in relaxation responses could not be linked to changes in arterial contractility to norepinephrine or histological alterations in the arterial wall. These findings suggest a promising therapeutic approach for minimizing reperfusion injury following acute limb ischemia.[20]

Pentoxifylline administration also reduced the systemic inflammatory response. In a study with rats that were clamped on their splenic vessels, pentoxyfilline was able to significantly reduce serum TNF-α, IL-6 and IL-10.[21] Administration of pentoxifylline 40 mg/kg dissolved in 0.9% normal saline solution up to 2 ml reduces the inflammatory index in ischemic reperfusion injury.[17]

Pentoxifylline in human studies

Pentoxifylline in intermittent claudication at a dose of 400 mg three times a day for 3 month can improve blood rheological properties by reducing plasma and whole blood viscosity, decreasing plasma fibrinogen, increasing erythrocyte distensibility, suppressing erythrocyte aggregation, reducing platelet aggregation, and suppressing neutrophil activation.[22–24] Pentoxifylline infusion 1000 mg as an inhibitor of free radical formation resulted in improvement of ischemic damage with an indicator of significant shortening of the half-life of transcutaneous oxygen pressure recovery.[25] Peripheral occlusive arterial disease patients receiving 400 mg pentoxifylline four times daily for six weeks showed significant improvements in erythrocyte deformability and a positive impact on microcirculatory blood fluidity.[26] Critical limb ischemia patients were treated with pentoxifylline infusion 600 mg twice daily consistently and experienced a significantly decreased pain at rest.[27]

Combination therapies

Recent studies have explored the efficacy of pentoxifylline in combination with other agents, such as vitamin

C. A study indicated that this combination therapy could further reduce lung damage due to ischemia-reperfusion injury, suggesting enhanced protective effects through synergistic mechanisms.[17]

Conclusion

Pentoxifylline appears to be a promising agent in the prevention and treatment of reperfusion injury across various organ systems. Its ability to inhibit PAF production, reduce inflammation, and improve hemorheological properties positions it as a valuable therapeutic option. Further clinical trials are warranted to establish optimal dosing regimens and confirm its efficacy in human subjects suffering from conditions associated with ischemia--reperfusion injury.

Conflict of interest
None to declare.

Funding
None.

Ethical statement
The study was conducted in accordance with Helsinki declaration.

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