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Original article

Oral N-acetylcysteine in the treatment of Raynaud's phenomenon secondary to systemic sclerosis: A randomized, double-blind, placebo-controlled clinical trial

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ABSTRACT

Objective: To evaluate the safety and efficacy of oral N-acetylcysteine (NAC) on digital microcirculation blood flow in patients with Raynaud's phenomenon (RP) secondary to systemic sclerosis (SSc).

Methods: This was a randomized, double-blind, placebo-controlled trial in which 42 patients with SSc received oral NAC at a dose of 600 mg tid (21 patients, mean age 45.6 ± 9.5 years) or placebo (21 patients, mean age 45.0 ± 12.7 years) for four weeks. The primary endpoint was the change in cutaneous microcirculation blood flow before and after cold stimulation measured by laser Doppler imaging (LDI) at weeks 0 and 4. The frequency and severity of RP and the number of digital ulcers were also measured at weeks 0 and 4. The adverse events were recorded in the fourth week.

Results: There was no significant change in digital blood flow assessed by LDI before or after cold stimulus after four weeks of NAC or placebo. Both groups showed significant improvement in the frequency and severity of RP attacks, with no difference between the two groups. At the end of the study, the placebo group had three digital ulcers, while the NAC group showed no ulcers. NAC was well tolerated and no patient discontinued the treatment.

Conclusions: NAC orally at a dose of 1800 mg/day showed no vasodilator effect on hands' microcirculation after four weeks of treatment in patients with RP secondary to SSc.

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N-acetilcisteína oral no tratamento do fenômeno de Raynaud secundário à esclerose sistêmica: Ensaio clínico randomizado, placebo-controlado e duplo-cego

Palavras-chave:
Esclerose sistêmica
Fenômeno de Raynaud
Estresse oxidativo
N-acetilcisteína
Tratamento

RESUMO

Objetivo: Avaliar a segurança e a eficácia da *N*-acetilcisteína (NAC) por via oral sobre o fluxo sanguíneo da microcirculação digital em pacientes com fenômeno de Raynaud (FRy) secundário à esclerose sistêmica (ES).

Métodos: Este foi um estudo randomizado, duplo-cego e placebo-controlado, no qual 42 pacientes com ES receberam NAC oral na dose de 600 mg, três vezes ao dia (21 pacientes, idade média 45,6 ± 9,5 anos) ou placebo (21 pacientes, idade média 45,0 ± 12,7 anos) durante quatro semanas. O desfecho primário do estudo foi: melhora no fluxo sanguíneo da microcirculação cutânea antes e após estímulo frio avaliado pelo *laser Doppler imaging* (LDI) nas semanas 0 e 4. A frequência e a gravidade do FRy e o número de úlceras digitais também foram avaliados nas semanas 0 e 4. Os efeitos adversos foram registrados na quarta semana.

Resultados: Não houve mudança significativa no fluxo sanguíneo digital avaliado pelo LDI antes ou depois do estímulo frio após quatro semanas de NAC ou placebo. Ambos os grupos apresentaram melhora significativa na frequência e gravidade dos ataques de FRy, sem diferença entre os dois. O grupo placebo apresentou três úlceras digitais enquanto o grupo NAC não apresentou úlceras ao final do estudo. NAC foi bem tolerada e nenhum paciente descontinuou o tratamento.

Conclusões: NAC por via oral na dose de 1.800 mg/dia não demonstrou efeito vasodilatador sobre a microcirculação das mãos após quatro semanas de tratamento em pacientes com FRy secundário à ES.

Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disease characterized by microvascular damage and fibrosis of skin and internal organs. Raynaud's phenomenon (RP) is one of the most common and earliest manifestations of SSc. It is characterized clinically by reversible episodes of vasospasm, usually limited to the hands and/or feet, and triggered by exposure to cold or emotional stress. In patients with RP secondary to SSc, not only functional abnormalities but also structural changes are present in the microcirculation, making the vasospastic events more severe and possibly leading to complications such as ulceration or tissue necrosis.[1]

The pharmacological treatment of the peripheral vascular disease secondary to SSc includes the use of vasodilators such as calcium channel blockers, nitrates and prostanoids, and vasoconstriction inhibitors such as endothelin receptor antagonists and α-adrenergic blockers. These agents reduce the frequency and severity of RP in patients with SSc.[2–5] However, they are not always completely effective and new therapeutic options are desirable.

Oxidative stress mediated by an increased activity of free radicals has been implicated in the pathogenesis and progression of SSc.[6,7] Repeated episodes of ischemia and reperfusion observed in these patients cause activation of endothelial cells, an imbalance in the relation between vasoconstrictor and vasodilator substances and an increase in reactive oxygen species and other toxic products. This cascade of events contributes significantly to the vascular damage associated with the disease and can also activate fibroblasts and immune cells.[6,8]

N-Acetylcysteine (NAC) is a thiol-containing compound (containing sulfhydryl) with a powerful antioxidant action. As a source of sulfhydryl groups in cells, NAC directly fights against free radicals through its interaction with the hydroxyl radical and hydrogen peroxide.[9] NAC also acts indirectly by inducing the synthesis of glutathione, whose main function is the removal of free radicals and the defense against oxidative stress.[9–11] Due to these properties, NAC has been used not only as a mucolytic agent in a variety of respiratory diseases, but also in other conditions characterized by a reduced level of glutathione and by oxidative stress. NAC was shown to improve the microcirculation blood flow in smokers and promote coronary vasodilation, besides increasing the endothelium-dependent peripheral dilation in patients undergoing cardiac catheterization and improving the endothelial function in dialysis patients.[10,12–14]

In patients with SSc, some open studies on high-dose intravenous (IV) NAC showed a significant improvement in blood perfusion and reduction in the frequency and severity of RP and in the number of active digital ulcers after its administration.[15–17] However, the IV route in continuous infusion and the high cost of this treatment considerably restrict its use. Only one clinical trial evaluated oral NAC in patients with SSc, but the vascular involvement has not been evaluated.[18]