Topical Application of Nitrosonifedipine, a Novel Free Radical Scavenger, Ameliorate the Ischemic Skin Flap Necrosis

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INTRODUCTION: Ischemic flap necrosis is often occurred by insufficient blood supply, which prolongs the treatment period and occasionally requires an additional surgery. Ischemic flaps generate an excess amount of free radicals which is regarded as a major factor of ischemic skin necrosis. Thus free-radical scavengers would be an effective drugs in improvement of flap survival. In our previous studies, we have reported nitrosonifedipine (NO-NIF), which is a photolytic compound of nifedipine, possesses a potent radical scavenging activity, and shows the favorable effects against vascular endothelial dysfunction and type 2 diabetic nephropathy. In this study, we evaluated the ameliorating effect of NO-NIF on the ischemic flap model mice.

MATERIAL AND METHODS: 9-10 weeks old Male C57BL/6 mice were divided into 2 groups, NO-NIF or control (n=6 in each group), respectively. A 1.0 × 3.0 cm cranially based random pattern flap was elevated on the dorsum of mice. NO-NIF 30 mg/kg or vehicle was injected subcutaneously immediate after the operation and once a day until evaluation. Seven days after surgery, the survival area was calculated as a percentage of the total flap area. To detect the oxidative stress, malondialdehyde (MDA) in the distal part of the flap at post-operative day 1 and 3 was measured by thiobarbituric acid reactive substances assay. Protein expression of p22phox, an essential component of NADPH-oxidase, in the flap was measured by western blotting.

RESULTS: At post-operative day 7, the flap survival area was significantly larger in the NO-NIF-treated mice than controls (78.29 ± 7.04% vs. 51.81 ± 6.85%, p=0.021). The amount of MDA significantly decreased in the NO-NIF-treated mice at post-operative day 3 (2.31 ± 0.28μmol/g protein vs. 4.21 ± 0.32μmol/g protein, p=0.001), whereas MDA was same level in the both groups at the post-operative day 1 (2.77 ± 0.61μmol/g protein vs. 2.96 ± 0.51μmol/g protein). In a manner consistent with MDA levels, protein expression level of p22phox was decreased in the NO-NIF-treated mice at post-operative day 3 (p=0.002).

CONCLUSIONS: We present the ameliorating effect of NO-NIF on ischemic flap survival. MDA and p22phox protein was decreased by NO-NIF treatment, which suggests the ameliorating effect was exerted via free radical scavenging. This investigation indicates that free-radical scavengers including NO-NIF are effective drugs in improvement of flap survival.