Simvastatin with niaspan improves neurological outcome after experimental intracerebral hemorrhage

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Introduction

Spontaneous intracerebral hemorrhage (ICH) is one of the most deadly forms of stroke and is usually associated with extensive cerebral tissue damage and neurological defects in most survivors. To date, surgical approaches for ICH treatment have been only modestly effective and no satisfactory drug treatment is used in clinical practice. One promising treatment for ICH is the promotion of neurogenesis and angiogenesis. Neurogenesis and angiogenesis may therefore contribute to brain repair and functional recovery, either through cell replacement or by indirect mechanisms.

Statins are a class of drugs that lower cholesterol levels by inhibiting the 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase enzyme which controls the rate of cholesterol production in our body. Statins exert relatively little effect on high-density lipoprotein (HDL) cholesterol, however, niacin (also called vitamin B3, nicotinic acid and vitamin PP) is an effective medication for increasing HDL. Elevated high-density lipoprotein cholesterol was shown to be correlated with higher collateral formation in coronary artery disease. In our previous study, statins have been shown to improve neurological recovery after ICH. Chen et al, have shown that Niaspan (a prolonged release formulation of Niacin) increases high-density lipoprotein cholesterol level and can enhance angiogenesis after stroke, which in turn is believed to improve functional outcome after stroke.

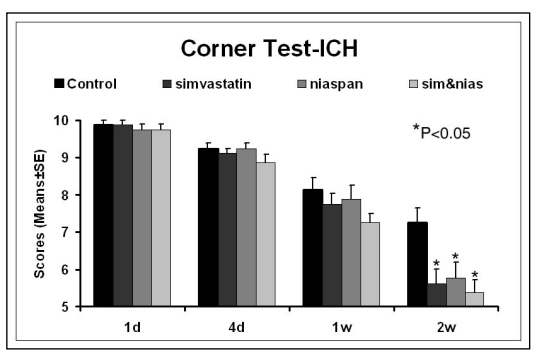
Niacin has been evaluated in combination with simvastatin in several clinical trials and has demonstrated efficacy and safety, with clinical improvement in multiple lipid parameters. The randomized, double-blind ARBITER 2 study demonstrated the benefits of combination of niacin and statin in inhibiting atherosclerosis. In animal models, combination treatment of stroke with niacin and simvastatin starting 24 h after MCAo has shown a significant decrease in axonal damage and in activated microglia. Nevertheless, in the recent trial AIM-HIGH, a slow-release form of niacin was found to have no effect on cardiovascular events and stroke risk in a group of patients with LDL levels already well-controlled by a statin drug. The trial was halted prematurely on evidence that the addition of niacin actually increased stroke risk in this group. The role of niacin in treating cardio-vascular risk remains controversial. Studies have not been performed in ICH and this study was designed to determine the mechanisms of action and efficacy of niacin and simvastatin in the experimental models of ICH so that they can be translated to address the critical clinical need.

Methods and Results

ICH model: Primary ICH was induced by direct infusion of 100 µL of fresh (nonheparinized) autologous whole blood into the right striatum adjacent to the SVZ at a constant rate of 10 µL/min. All rats received daily intraperitoneal injections of bromodeoxyuridne (BrdU; 100mg/kg; Sigma, St. Louis, MO) for 14 consecutive days.

Statin and Niaspan treatments: The ICH animals were randomly assigned to experimental groups (n=8/group). Group 1 received 2 mg/kg simvastatin, group 2 received 40 mg/kg niaspan, group 3 received both 2 mg/kg simvastatin and 40 mg/kg niapsan, and group 4 (control group) received the same volume of phosphate buffered saline (PBS) starting 24-hour daily for 7 days by oral gavage.

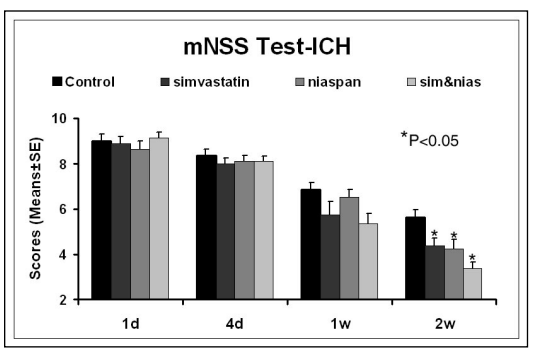
Neurobehavioral testing: Functional outcome was assessed using a cornering test and modified neurological severity score (mNSS) at 1, 4, 7, and 14 days after ICH. The cornering test measures the number of times that an animal turns to the right or left when placed in a corner (the normal state being 50%). The mNSS is a composite score of motor, sensory, balance, and reflex measures that are used to assess neurological functions with higher scores implying greater neurological injury.

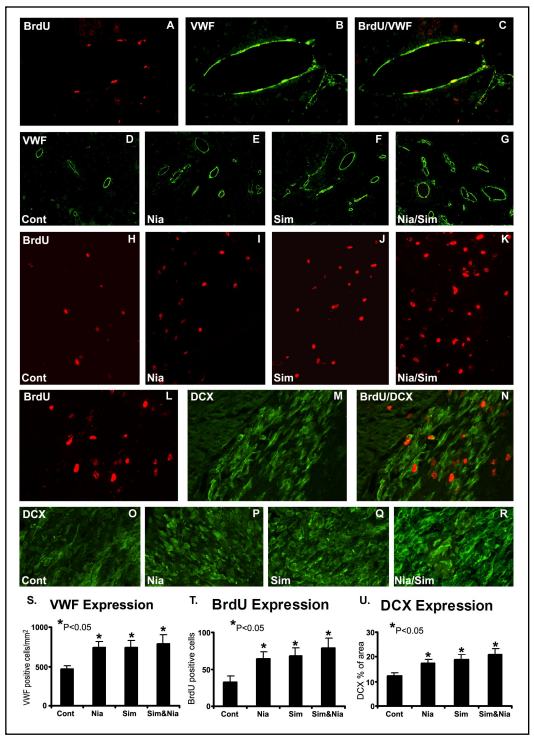


Histology and immunohistochemistry: Rats were sacrificed after 2 weeks post-ICH. Semiquantitative immunostaining measurements of BrdU (a marker for proliferation cells), doublecortin (DCX; a marker for migrating neuroblasts) and von Willebrand factor (vWF, a marker for endothelia function) were performed. BrdU-positive cells and DCX-positive areas were counted in the SVZ. vWF–positive vessels were estimated in the ipsilateral boundary area around the hematoma. All values are expressed as Mean ± SEM. Results between treatment and control groups were compared using an analysis of variance (ANOVA) procedure with significance inferred at $p < 0.05$.

Conclusion and Discussion

1. Simvastatin at a dose of 2 mg/kg, niaspan at a dose of 40 mg/kg, and combination treatment starting 24 hours post-ICH and persisting through Day 7 improve neurological functions 2 weeks after ICH, respectively.
2. The underlying mechanism may be associated with increasing neuronal and endothelia cell proliferation after ICH.
3. The combination treatment was equal or slightly more effective than single treatment with simvastain and niaspan.
4. The treatments with simvastatin and/or niaspan were safe and effective. There was no further hemorrhage found in either group in this study.
5. The dose used was not optimal and the dose dependency of the treatment regimens should be investigated further in order to most effectively translate these findings toward human trials.





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