Nicotine Replacement Therapy After Subarachnoid Hemorrhage Is Not Associated With Increased Vasospasm

Raphael A. Carandang, MD; Bruce Barton, PhD; Guy A. Rordorf, MD; Christopher S. Ogilvy, MD; John R. Sims, MD

Background and Purpose—A significant number of patients with aneurysmal subarachnoid hemorrhage are active smokers and at risk for acute nicotine withdrawal. There is conflicting literature regarding the vascular effects of nicotine and theoretical concern that it may worsen vasospasm. The literature on the safety of nicotine replacement therapy and its effects on vasospasm is limited.

Methods—A retrospective analysis was conducted of a prospectively collected database of aneurysmal subarachnoid hemorrhage patients admitted to the neurointensive care unit from 1994 to 2008. Paired control subjects matched for age, sex, Fisher score, aneurysm size and number, hypertension, and current medication were analyzed. The primary outcome was clinical and angiographic vasospasm and the secondary outcome was Glasgow Outcome Score on discharge. Conditional logistic models were used to investigate univariate and multivariate relationships between predictors and outcome.

Results—Two hundred fifty-eight active smoking patients were included of which 87 were treated with transdermal nicotine replacement therapy. Patients were well matched for age, sex, gender, Fisher score, aneurysm size and number, hypertension, and current medications, but patients who received nicotine replacement therapy had less severe Hunt-Hess scores and Glasgow coma scores. There was no difference in angiographic vasospasm, but patients who received nicotine replacement therapy were less likely to have clinical vasospasm (19.5 versus 32.8%; \( P = 0.026 \)) and a Glasgow Outcome Score <4 on discharge (62.6% versus 81.6%; \( P = 0.005 \)) on multivariate analysis.

Conclusions—Nicotine replacement therapy was not associated with increased angiographic vasospasm and was associated with less clinical vasospasm and better Glasgow Outcome Score scores on discharge. (Stroke. 2011;42:3080-3086.)

Key Words: neurocritical care ■ nicotine ■ subarachnoid hemorrhage ■ vascular tone regulation ■ vasospasm

Cigarette smoking is an established risk factor for aneurysmal subarachnoid hemorrhage and vasospasm. Up to one third of patients with aneurysmal subarachnoid hemorrhage admitted to the hospital are active smokers and are at theoretical risk for acute nicotine withdrawal on abrupt forced discontinuation of cigarette smoking on admission to the hospital. Symptoms of nicotine withdrawal described in the literature include anxiety, restlessness, difficulty concentrating, drowsiness or insomnia, headaches, irritability, depression, and even delirium and can start as early as 3 hours after cessation but typically peak at 48 to 72 hours and are dependent on the chronicity and amount of cigarettes smoked. These symptoms and timeline are disadvantageous in patients with subarachnoid hemorrhage (SAH) because they can be difficult to distinguish clinically from worsening SAH symptoms. Also, peak withdrawal symptoms can coincide with the occurrence of early cerebral vasospasm. Despite a good proportion of smokers among admitted patients and the concern for delirium as described in case reports, the true impact of nicotine withdrawal in the critically ill population is not well described or characterized and thus the current practice of nicotine replacement therapy is not uniform.

Review of the Literature

Cigarette smoke contains >4000 substances and although nicotine accounts for many of the known physiological effects and addictive properties of cigarettes, it is not clear what effects nicotine itself has on the vasculature. Numerous experimental studies have investigated the effects of smoking and nicotine on various vascular beds and in various species. Much of the research has been on noncerebral vessels, including skin and mesenteric, coronary, and extracranial...
carotid vessels. Some describe a vasoconstrictor effect on the vessels studied through a variety of mechanisms; however, studies looking at the cerebral vasculature have not been equivalent. Studies on porcine basilar arteries by Mayhan et al., in which they gave acute nicotine infusions and measured in vivo diameters of the arteries as well as superoxide anion production, found that nitric oxide (NO)-dependent but not NO- independent vasodilation was impaired and that there was increased production of superoxide anion in the basilar artery with acute nicotine infusion.11

Koide and colleagues studied canine basilar arterial rings that were exposed to nicotine for 1 hour with endothelium-intact and de-endothelialized samples and no contractile responses were seen on isometric tension studies using uridine triphosphate in either group.12 They also measured protein kinase C activity, measured substance P-induced vasodilation and NO synthesis, and concluded that nicotine attenuated endothelium-dependent vasodilation by substance P, decreased NO synthesis, and increased protein kinase C activity but that ultimately nicotine does not cause vasoconstriction in canine basilar arteries; however, it may impair endothelial function and enhance protein kinase C activity resulting in an artery prone to vasoconstriction.

Si and Lee, also studying porcine basilar arteries and feline middle cerebral arteries, demonstrated that nicotine acts on 

\[ \alpha_7 \] -nicotinic acetylcholine receptors located on the perivascular postganglionic sympathetic nerve terminals and releases norepinephrine that acts on \[ \beta_2 \] adrenergic receptors resulting in release of NO and that nicotine-induced NO-mediated vasodilation was dependent on intact perivascular sympathetic adrenergic innervation originating in the superior stellate ganglion.13,14

Iida and colleagues studied cerebral pial vessels in rats after cigarette smoke inhalation and nicotine infusion and found a biphasic response with initial vasoconstriction followed by vasodilation from cigarette smoke inhalation. In contrast, nicotine infusions resulted only in vasodilation. Using a number of antagonists, they determined that the vasoconstricting effect was likely related to thromboxane and possibly other agents in cigarettes and that nicotine in contrast had a vasodilating effect on the pial arterioles.15

Traystman in an accompanying editorial states that the difficulty of investigating the effects of cigarette smoke is the multitude of substances in cigarettes, possible interactions or synergistic effects, and other modulating factors such as hypoxemia and carboxyhemoglobinemia and its effects, making the elucidation of underlying mechanisms challenging.16 Other authors also emphasize that cigarette smoking is not equivalent to nicotine consumption and that many of the harmful effects of cigarette smoking are not likely secondary to nicotine.

All of these studies argue against nicotine having direct vasoconstricting effects in the cerebral vasculature, but some suggest that nicotine may affect endothelial function and NO synthesis and protein kinase C activity. Miller and colleagues looked at 3 different dosages (11, 22, and 44 mg) of transdermal nicotine patches and their effects on the canine aorta, coronary arteries, and saphenous veins using organ chamber experiments and found that maximal contractions were not affected by nicotine. They also measured nicotine and cotinine levels, NO synthase activity, and used various agonists to evaluate endothelium-dependent relaxations and had several pertinent findings: (1) at 2 weeks of treatment, there was no difference in circulating NO levels, total and calcium-dependent NO synthase activity, or endothelium dependent relaxations to \[ \alpha_2 \] adrenergic agonists, adenosine 5'-diphosphate, and calcium ionophore A-23187; (2) after 5 weeks, NO levels decreased, total and calcium-dependent NO synthase activity increased, and endothelium dependent relaxation to \[ \alpha_2 \] adrenergic agonists, adenosine 5'-diphosphate, and calcium ionophore A-23187 were decreased with dose-response curves shifted to the right; and (3) acetylcholine caused concentration-dependent relaxation in all arteries with endothelium and application of NO inhibitor shifted its dose–response curve to the right. Much of these findings were seen in the 22-mg dose patches. They concluded that effects of transdermal nicotine on the coronary endothelial function depend on the time, duration, and agonist used to stimulate the endothelial cells and emphasized that in further evaluation of nicotine and its effects, close attention needs to be paid to the vessels studied, mode of delivery, dose, and duration of treatment.17

More recently, Uchida and Hotta studied cortical blood flow using laser Doppler flowmetry in rats after injection of nicotine boluses focusing on the up- and downregulation of nicotinic receptors and their influence on cortical vessel dilatation.18 They describe an increase in cortical blood flow independent of systemic blood pressure with nicotine infusion mediated by NO after activation of nicotinic receptors probably of the \[ \alpha_4\beta_2 \]-like subtype in the basal forebrain nuclei and the cortex. They suggest that NO may be released by cholinergic neurons (and possibly glial and endothelial cells in the central nervous system) because they have demonstrated nicotinic receptors and NO-positive cortical neurons in the proximity of cortical blood vessels using NO synthase-immunoreactivity assays. They also describe regional differences in blood flow regulation to different areas of the brain that are dose-related as well as differences in nicotinic receptor types for large cranial vessels versus cortical vessels such as \[ \alpha_7 \] -nicotinic acetylcholine receptors activation causing porcine basilar artery vasodilation. Lastly, they found a reduction in the vasodilatory effect of nicotine with longer-term (>14 days) administration indicating a decrease in signal transmission through nicotinic receptors that was dependent on dose and duration, suggesting that receptor desensitization and upregulation of receptors may be occurring. They surmise from their data and others that long-term nicotine treatment decreases nicotine-evoked release of acetylcholine and functional activity of \[ \alpha_4\beta_2 \]-like \[ \alpha_7 \] -nicotinic acetylcholine receptors. They extended their investigation to older rats and found a decrease in the blood flow response to nicotine in the very old rats with a higher threshold and hypothesize that this may due to a decrease in nicotinic receptors in the cortex with aging. See Table 1 for a summary of studies investigating the effects of nicotine on the cerebral vasculature.
Research studies have uncovered neurogenic modulation of inflammation, which is vagally mediated and that which involves acetylcholine acting on \( \alpha 7 \) nicotinic acetylcholine receptors. Nicotine has been found to be an efficient inhibitor of proinflammatory cytokine production and inflammatory signaling acting on a host of immune cells and has subsequently been investigated as a therapeutic target in inflammatory diseases like ulcerative colitis and sepsis. Nicotine acting on \( \alpha 7 \)-nicotinic acetylcholine receptors also triggers a spectrum of anti-inflammatory pathways involving inhibition of nuclear factor \( \kappa B \) activation and Jak2/STAT signal transduction and has been speculated to have neuroprotective effects against Abeta and glutamate toxicity and may prevent apoptosis by activating the Janus kinase-2, phosphatidylinositol 3-kinase, and Akt signaling pathways.

There is currently much investigation and interest around the possible neuroprotective effects of nicotine in degenerative neurological diseases. The current evidence suggests that nicotine has multiple complex effects but that it does not directly cause vasoconstriction in cerebral vessels and may have anti-inflammatory, neuroprotective, and neurogenic vasodilatory effects that are mediated by NO and endothelium-related mechanisms through nicotinic acetylcholine receptors in large intracranial and cortical vessels and that the dose, timing, and duration of nicotine administration as well as the age of the treated cohort are important factors (Figure).

Nicotine replacement therapy (NRT) is a well-established therapy to effect smoking cessation with strong evidence from multiple randomized clinical trials. Current clinical

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Table 1. Studies Investigating Vascular Effects of Nicotine

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<thead>
<tr>
<th>Year</th>
<th>Authors</th>
<th>Specimen</th>
<th>Methodology</th>
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| 2009 | Mayhan et al | Porcine basilar arteries | Measured diameters of arterial rings and superoxide anion production after acute nicotine infusion | (1) No direct vasoconstrictor effect  
(2) NO-dependent but not NO-independent vasodilation was impaired  
(3) Increased production of superoxide anion in the basilar artery |
| 2005 | Koide et al | Canine basilar arteries | Nicotine exposure of endothelium intact and de-endothelialized arterial rings for 1 h, measurement of contractile responses and protein kinase C activity after uridine triphosphate | (1) No contractile responses  
(2) Attenuation of endothelium dependent vasodilation by substance P  
(3) Decreased NO synthesis  
(4) Increased protein kinase C activity |
| 2002 | Si and Lee | Porcine basilar arteries, feline middle cerebral arteries | Choline and nAChR agonists administered to in vitro tissue baths after contraction with U-46619, confocal microscopic studies | (1) Choline and nicotine caused calcium influx and released norepinephrine that act on \( \beta \) adrenergic receptors  
(2) Presynaptic \( \alpha 7 \)-nicotinic acetylcholine receptors mediate nicotine-induced nitric oxidergic neurogenic vasodilation  
(3) NO-mediated vasodilation dependent on intact perivascular sympathetic adrenergic innervation |
| 1998 | Iida et al | Rodent cerebral pial vessels | Vasomotor response to smoking inhalation and nicotine infusion | (1) Biphasic response to smoke  
(2) Vasodilatory response to nicotine  
(3) Vasocostriction from thromboxane or other agents in smoke |
| 2000 | Miller et al | Canine aorta, coronary arteries, saphenous veins | Organ chamber experiments to measure contractions, measured cotinine, nicotine and NO activity after 11, 22, and 44 mg of transdermal nicotine exposure | (1) No effect at 2 wk  
(2) At 5 wk, NOS activity increased, NO levels, endothelium-dependent relaxation to \( \alpha \)-adrenergic agonists, ADP, and A-23187 all decreased  
(3) Ach caused concentration-dependent relaxation of all arteries |
| 2009 | Uchida and Hotta | Rodent cortical blood flow, porcine basilar artery | Laser Doppler flowmetry after injection of nicotine boluses | (1) Increase in cortical blood flow with nicotine infusion  
(2) Mediated by NO after activation of \( \alpha 4\beta 2 \) Ach receptors in basal forebrain  
(3) Regional differences in blood flow  
(4) \( \alpha 7 \) nAChr activation causing basilar artery vasodilation  
(5) Reduction in vasodilatory effect with chronicity |

nAChr indicates \( \alpha 7 \)-nicotinic acetylcholine receptors; NO, nitric oxide; NOS, nitric oxide synthase; ADP, adenosine 5’-diphosphate; Ach, acetylcholine.
practice deems NRT safe even in patients with cardiac disease except those with active unstable angina or recent myocardial infarction. The literature is extremely limited but most recent studies in the intensive care unit population report no increase in mortality in the medical intensive care unit and neuroscience intensive care units, although patients undergoing cardiac surgery did have NRT-associated increases in postoperative mortality and some authors warn that NRT is not harmless and that the further prospective study is necessary. A recent study in patients with SAH even found a mortality benefit at 3 months with NRT.

Materials and Methods

Our aim was to investigate if NRT had any effects on clinical and angiographic vasospasm as well as outcomes. Using a prospectively collected Institutional Review Board-approved database of patients admitted to the Massachusetts General Hospital for the management of SAH, we retrospectively identified all patients with SAH who were hospitalized between January 1, 1994, and December 31, 2008, and met the following inclusion criteria: (1) age >18 years; (2) survival through the first 72 hours of hospitalization; (3) documented aneurysm as the cause of SAH; (4) aneurysm repair by either surgical clipping or endovascular coiling within 72 hours of ictus; and (5) active smoking at the time of admission to the hospital. Two patient groups were subsequently identified: (1) patients who were treated with transdermal NRT; and (2) those who were not.

A total of 1486 patients with SAH were admitted to the neurosciences intensive care unit at Massachusetts General Hospital from 1994 to 2008 and were enrolled in a prospective database of which 352 were identified as active smokers. Eighty-seven patients were treated with transdermal NRT. Paired control subjects from the cohort of active smoking patients who were not treated with NRT were matched for age, sex, Fisher score, aneurysm size and number, hypertension, current medications, and epoch of treatment (≤5 years) and comprised the control cohort of 171 patients for a total enrolled cohort of 258 patients. Patients were excluded if SAH was nonaneurysmal, they were nonsmokers, or if their smoking histories were unreliable or unavailable. Patients were considered active smokers if they had smoked any amount of daily tobacco up to the day of admission. The patients who were given transdermal nicotine patches ranged from doses of 7 to 21 mg and were initiated at the discretion of the attending neurointensivist and were continued until discharge.

All patients with SAH were treated according to a standardized clinical protocol. They were assigned a Hunt and Hess (HH) clinical score and Fisher grade based on their initial clinical presentation and head CT imaging. Identified intracerebral aneurysms were treated with either surgical clipping or endovascular coiling within 24 to 72 hours of admission. The decision to clip or coil was based on collective decision-making among neurosurgery, neurointerventional, and neurocritical care teams. Patients with no visible aneurysm on conventional 4-vessel cerebral angiography underwent repeat diagnostic cerebral angiography 7 days after presentation. Patients were monitored in the neurosciences intensive care unit until resolution of vasospasm or posthemorrhage Day 10. Continuous blood pressure monitoring was done with an arterial catheter and continuous central venous pressure monitoring with a central venous catheter. Extraventricular drains were placed before or during aneurysm repair in patients with clinical and radiographic evidence of hydrocephalus. Phenytoin was administered on hospital admission and discontinued after the aneurysm has been secured or if the patient was awake and following commands. All patients were treated with a 21-day course of oral nimodipine. Hyperthermia was treated with acetaminophen and surface cooling to euthermia. Euvolemia with target central venous pressure of 8 to 10 mm Hg was maintained. Patients received daily or every other day transcranial Doppler ultrasound screening for vasospasm. All patients with clinical, transcranial Doppler, or angiographic vasospasm were treated with hemodynamic augmentation (systolic blood pressure >160 mm Hg) and hypervolemia (central venous pressure >8 cm H₂O) until the resolution of clinical and angiographic vasospasm. Those with medically refractory vasospasm were treated with balloon angioplasty or intra-arterial infusion of vasodilators.

Medical records of included patients were reviewed. The following demographic and clinical characteristics were recorded: age, sex, HH grade, Fisher grade, aneurysm location and size, number of aneurysms, method of aneurysm repair, medical history of hypertension, current medications including selective serotonin reuptake
inhibitor, β-blocker, calcium channel blocker, angiotensin-converting enzyme inhibitor, and statin and aspirin use.

Angiographic vasospasm was diagnosed by conventional digital subtraction angiography and reviewed by the interventional neuroradiology, diagnostic neuroradiology, neurology, and neurosurgery teams. Clinical or symptomatic vasospasm was defined as any transcranial Doppler peak systolic velocity >200 cm/s or mean systolic velocity >120 cm/s and radiological evidence of vessel narrowing >25% from baseline or >50% from normal associated with clinical deterioration in the absence of other causes such as worsening hydrocephalus, rebleeding, seizures, infection, other systemic illness. Adjudication of clinical vasospasm was done by the team of critical care neurologists, neurosurgeons, and interventional neuroradiologists caring for the patients.

Good and poor outcomes were defined as Glasgow Outcome scores of <4 and ≥4, respectively, and was based on physical therapy notes recorded at the time of discharge.

Percentages were calculated in the usual way. Pearson χ² tests for bivariate relationship between case/control and outcomes, treatments, or baseline characteristics were calculated without the continuity correction. Conditional logistic models were fit to the data to investigate multivariate relationships between predictors and the outcome, conditioning on the 1: n matching present in the study. We investigated 4 outcomes: Glasgow Outcomes Scale (categorized as "good result" versus all other results), any vasospasm (VSP; present by any indication; categorized as yes versus no), symptomatic VSP (VSP with physical decline; yes versus no), and angiographic VSP (VSP with angiographic evidence; yes versus no). For the Glasgow Outcomes Scale, we modeled "good result" as the outcome of interest. For the VSP outcomes, we modeled "yes" as the outcome of interest. ORs for the predictors were calculated by exponentiating the parameters from the logistic model. Probability values were calculated as the test of the parameter=0. All calculations were performed with SAS (Version 9.2).

Results
The mean age of the cohort was 50.61 ± 11.8 years; 168 (65.1%) patients were women. Eighty-seven (33.7%) had a history of hypertension. Twenty-one (8.1%) were taking calcium channel blockers, 54 (20.9%) β-blockers, 34 (13.2%) angiotensin-converting enzyme inhibitors, 19 (7.4%) were taking statins, 38 (14.7%) were on aspirin, and 52 (20.2%) were taking selective serotonin receptor inhibitors. A poor HH grade (>3) was documented in 47 (18.2%) and poor Glasgow Coma Score (<8) was seen in 17 (6.6%) patients. Majority were classified as Fisher Grade 3 on admission CT (185 [72%]). Half developed angiographic VSP (129 [50%]) and 73 (28.3%) had clinical VSP. Of the 258 patients included, 14 (5.4%) died and 178 (69%) had a good outcome defined as a Glasgow Outcome Score >4.

There were no significant differences between the NRT and control subjects in age, percentage of women, hypertension, aneurysm size and number, Fisher grade, and modified Fisher grades. There were, however, significantly better HH scores, Glasgow Coma Scale scores, and World Federation of Neurological Surgery scores in the NRT group indicating less severe clinical disease in those that received NRT. See Table 2 for comparative demographic data and baseline characteristics.

On univariate analysis there was no significant difference in the occurrence of angiographic VSP between those that received NRT and those that did not; however, the proportion of patients that had clinical VSP was significantly lower in the patients who had NRT. Consistent with previous studies, Fisher grading (OR, 2.07; 95% CI, 1.16 to 3.69; P = 0.0132) was strongly associated with the development of vasospasm and HH grade (OR, 0.51; 95% CI, 0.31 to 0.84; P = 0.007 for good outcome) was strongly associated with poor outcome. Age was associated with outcomes with older patients doing worse (OR, 0.85; 95% CI, 0.75 to 0.98; P = 0.024). The proportion of patients with good outcomes (Glasgow Outcome Score >4 on discharge) was significantly higher in the patients who received NRT (OR, 3.05; 95% CI, 1.41 to 6.62; P = 0.005). Length of stay was significantly shorter for the NRT group. Of the patients who received NRT, 2 (2.3%) died versus 12 (7%) in the control group (Table 3).

On multivariate analysis after adjustment for Fisher grades, the NRT group had a significant likelihood of less clinical vasospasm (adjusted OR, 0.45; 95% CI, 0.23 to 0.88; P = 0.019) when compared with control subjects. Multivariate analysis for outcomes also showed NRT-treated patients were more likely to have good outcomes even after adjusting for Glasgow Coma Scale and World Federation of Neurological Surgery scores (adjusted OR, 2.17; 95% CI, 1.19 to 3.97; P = 0.012).

Discussion
In this study, we determined the impact of NRT on clinical and angiographic vasospasm as well as outcomes in patients

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SSRI indicates selective serotonin receptor inhibitor; ACE, angiotensin-converting enzyme.

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<th>Table 3. Outcomes</th>
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GOS indicates Glasgow Outcome Score.
with aneurysmal SAH who are active smokers. This is the second study to demonstrate that NRT administered acutely is not associated with angiographic VSP and the first to demonstrate less clinical vasospasm in patients with aneurysmal SAH who received NRT. We chose angiographic VSP as one of the primary outcomes because it is easily and objectively measurable and strongly correlates with cerebral infarction after SAH but chose clinical VSP as the major outcome because along with delayed cerebral ischemia because it is the most clinically relevant and has been demonstrated to be associated with worse functional outcomes as measured by the Lawton Activities of Daily Living scale, cognitive impairment, and quality of life and drives real-time acute care management decisions. Definitions among studies have been inconsistent and a multidisciplinary research group has recently proposed that in observational and clinical studies of aneurysmal SAH, the outcomes measured should preferably be delayed cerebral ischemia and functional outcome. Delayed cerebral ischemia is superior in that in multivariate analysis, it is the only outcome associated with death and disability as measured by modified Rankin Scale scores. In many centers, however, repeat CT imaging and MRI are not practical or routine unless a patient has persistent deficits and needs further clinical investigation.

We also demonstrate better outcomes as measured by the Glasgow Outcome Score on discharge in patients who received NRT. Although efforts were made to correct for the more severe clinical disease in the control group as reflected by HH and Glasgow Coma Scale scores in the multivariate analysis model, it is still possible given the multiple and complex factors in the care of these critically ill patients that clinical severity resulted in worse clinical outcomes in the control group. Mortality was higher in the control group but given the small total number of deaths and imbalance in clinical severity and multiple confounding factors possibly unaccounted for, it would be difficult to attribute the mortality benefit to NRT alone.

We can conclude like the previous study by Seder et al that NRT is safe in patients with aneurysmal SAH and does not worsen vasospasm. Our results also demonstrate possible therapeutic effects of NRT in attenuating clinical vasospasm and improving outcome. Research continues to improve our understanding of the pathogenic mechanisms underlying clinical VSP and in parallel has improved our knowledge of nicotine’s physiological and cellular effects making it plausible as a therapeutic target for future study.

Numerous limitations of our study are inherent to its retrospective nature, including (1) imperfect data that did not allow us to quantify the cigarette consumption of the subjects or the degree of delirium and other medical complications that may have influenced outcomes as well as the exact dosages of the nicotine patches, which would otherwise allow for a dose–effect analysis; (2) limited follow-up that did not include better functional outcome measures such as modified Rankin Scale scores and longer-term follow-up after discharge; (3) incomplete follow-up neuroimaging preventing us from determining delayed cerebral ischemia; and (4) selection bias that may affect all retrospectively analyzed studies.

Conclusions

NRT was not associated with increased angiographic VSP and was associated with less clinical vasospasm and better Glasgow Outcome Scores on discharge. A prospective study in larger cohorts of patients better matched for clinical severity is needed to validate whether NRT has beneficial effects on clinical VSP and clinical outcome.

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References

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