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ORIGINAL ARTICLE

Transdermal Nicotine Replacement Therapy in Cigarette Smokers with Acute Subarachnoid Hemorrhage

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Abstract
Background We evaluated the safety of nicotine replacement therapy (NRT) in active smokers with acute (aneurysmal) subarachnoid hemorrhage (SAH).
Methods A retrospective observational cohort study was conducted in a prospectively collected database including all SAH patients admitted to an 18-bed neuro-ICU between January 1, 2001 and October 1, 2007. Univariate and multivariable models were constructed, employing stepwise logistic regression. The primary endpoint was 3-month mortality. Delayed cerebral ischemia (DCI) due to vasospasm, angiographic and TCD evidence of vasospasm, and delirium were secondary endpoints.
Results Active cigarette smokers admitted with SAH included 128 that received NRT and 106 that did not. Patients were well-matched for age, admission Hunt-Hess Grade, radiographic findings, and APACHE II scores, but those who received NRT were more likely to be heavy smokers (>10 cigarettes daily), diabetic, heavy alcohol users, and to have cerebral edema on admission. NRT was associated in multivariate analysis with a lower risk of death at 3 months (OR 0.12, 95% CI 0.04–0.37, $P < 0.001$). There were no differences in the frequency of DCI and most other medical complications, but delirium (19 vs. 9%, $P = 0.006$) and seizures (9 vs. 2%, $P = 0.024$) were more common in patients who received NRT.
Conclusions Despite vasoactive properties, administration of NRT among active smokers with acute SAH appeared to be safe, with similar rates of vasospasm and DCI, and a slightly higher rate of seizures. The association of NRT with lower mortality could be due to chance, to uncontrolled factors, or to a neuroprotective effect of nicotine in active smokers hospitalized with SAH, and should be tested prospectively.

Keywords Subarachnoid hemorrhage · Hemorrhagic stroke · Nicotine · Neurocritical care · Aneurysm

Introduction

Smoking is an important risk factor for aneurysmal subarachnoid hemorrhage (SAH), and 40–60% of all patients admitted with spontaneous SAH are active cigarette smokers [1–3]. Being an active smoker at the time of hospital admission for SAH is a risk factor for the development of delayed cerebral ischemia (DCI) from vasospasm [2, 4, 5]. For smokers presenting with SAH, admission to the hospital reflects a period of acute and involuntary smoking cessation, and they are therefore at risk for acute nicotine withdrawal [6]. Many of these patients will resume tobacco use after hospital discharge [7].

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Nicotine replacement therapy (NRT) is often prescribed to hospitalized patients [8] because withdrawal from nicotine can cause agitation, anxiety, dysphoria, and in severe cases, frank delirium [6, 9, 10]. Although the physiological impact of nicotine withdrawal in critically ill patients has not been well described, delirium is associated with increased mortality, longer hospital and ICU stay, and an increased cost of healthcare [11–14]. The safety and efficacy of NRT for hospitalized patients with acute cardiac disease is controversial, with many but not all studies demonstrating that NRT is safe and promotes long-term smoking cessation [15–19].

The safety of nicotine replacement in medical and surgical ICU patients was recently challenged in a retrospective case–control study finding increased risk of death among critically-ill smokers that received NRT compared to those with similar severity of illness who did not [20]. In this study it was unclear whether nicotine itself posed a danger to these patients, or if the difference in mortality was due to uncontrolled variables, such as active heavy smoking. The lead author of that paper subsequently presented a second, larger cohort of similar patients in abstract form, refuting her earlier findings [21]. A second case–control study in active smokers receiving NRT after coronary artery bypass grafting surgery demonstrated a strong trend toward higher mortality with therapy—a difference that was statistically significant in a subgroup of patients undergoing off-pump CABG. These authors recommended extreme caution with NRT in the peri-CABG population [22].

The physiological effects of nicotine are complex. Acute hemodynamic effects include an increase in heart rate, blood pressure, and cardiac output. In the brain, nicotine has both vasodilator and vasoconstrictor properties, though animal models suggest that the most important effect of chronic nicotine exposure is inhibition of cerebral endothelial responsiveness to nitric oxide—a potent vasodilator [23–26]. Some experimental data suggest that nicotine may directly injure the endothelium, through mechanisms that are poorly understood [27, 28]. Theoretically, nicotine administration during the acute phase of SAH might increase the risk of developing complications related to cerebral vasospasm.

The safety of NRT in acute, aneurysmal SAH is unknown. Between 2001 and 2007, NRT was variably prescribed, according to attending physician preference and often in response to delirium, to smokers in the Columbia University Medical Center (CUMC) subarachnoid hemorrhage outcomes project (SHOP) database. We compared the mortality, incidence of DCI from vasospasm, and other hospital complications in smokers who received NRT during the acute phase of their illness, to smokers that did not. Nonsmokers are shown in our analyses for purposes of comparison.

Materials and Methods

Patient Population

Six hundred and five patients with SAH admitted to the Columbia University Medical Center (CUMC), Neurological Intensive Care Unit, between January 1, 2001 and November 9, 2007 were enrolled in the prospective CUMC SHOP database. The study was approved by the CUMC Institutional Review Board, and informed consent for participation was obtained from patients or their surrogates at the time of neurological intensive care unit (NICU) admission. Patients were diagnosed with SAH by computed tomography (CT) scan, or by the presence of xanthochronia in the cerebral spinal fluid. Patients with ruptured aneurysms and with crypogenic SAH were included; those under 18 years or with SAH from trauma, arteriovenous malformations, or other secondary causes, were excluded. Patients who died within 3 days of admission were excluded from the present analysis. Patients were categorized as active smokers if they used any amount of daily tobacco up to the day of ictus.

Intervention

NRT (21 mg of nicotine given via a daily transdermal patch) was started on hospital admission for the prevention or treatment of nicotine withdrawal, at the discretion of the attending neurointensivist, and in all cases was continued after discharge. NRT was considered to have been administered if initiated within 14 days of ictus.

Clinical Management

Medical management was directed by one of four full-time neurointensivists who covered the NICU. All patients received 0.9% normal saline at a dose of 1 ml/kg/h, supplemental 5% albumin solution to maintain central venous pressure above 5 mmHg, and 60 mg of nimodipine every 4 h. Mechanically ventilated patients were sedated with propofol, in combination with fentanyl or midazolam, to promote comfort and ventilator synchrony, with interruption performed at least twice daily for neurological examination. Symptomatic DCI, intracranial hypertension, fever, anemia, and hyperglycemia were treated according to standardized protocols as previously described [29–31].

Clinical Data

Demographic data (age, sex, and race/ethnicity), social history (tobacco, cocaine, and alcohol use) and medical history were obtained through patient and family interviews on admission. Neurologic and medical status at

onset was assessed with the Glasgow Coma Scale (GCS), the Hunt-Hess Scale, the National Institutes of Health Stroke Scale (NIHSS), and the Acute Physiology and Chronic Health Evaluation-2 (APACHE-2) Scale. An admission physiologic derangement score was calculated by subtracting the GCS, age, and chronic health elements from the APACHE-2 score (range 0 = no physiological derangement, 71 = maximal physiological derangement). Admission and follow-up CT scans were independently evaluated by a study neurointensivist for the amount and location of blood, the presence of focal or global cerebral edema and hydrocephalus, or infarction. Transcranial Doppler ultrasonography was performed daily or every second day, and angiography was performed between SAH days 5–10 as clinically indicated to evaluate the presence of vasospasm. DCI was defined as clinical deterioration or cerebral infarction due to vasospasm, with adjudication by the research team in a weekly conference [32]. Delirium was defined as the acute onset and a fluctuating course of symptoms of agitation, inattention, and either confusion or an altered level of consciousness [33]. Other hospital complications were defined by specific criteria as previously described [34], and recorded during a review of each patient's clinical course at the end of hospitalization.

Outcome Assessment: Statistical Analysis

Data analyses were performed with commercially available statistical software (SPSS, version 15.0, SPSS Inc.). Admission demographic, clinical and radiographic variables, and medical complications during the course of hospitalization were tested for associations using univariate ANOVA for continuous variables and the chi-square test for categorical variables. To assess the effect of NRT on mortality, a multivariable model employing a backward stepwise selection procedure was created, with previously identified risk factors for mortality in our database used as covariates. Significance was judged at $P \leq 0.01$ to account for multiple comparisons.

Results

Forty-one percent of 569 patients who survived for at least 3 days were active smokers (Fig. 1). Fifty-five percent of those smokers received NRT, and 45% did not. The NRT and non-NRT cohorts were similar as regards demographics, past medical history, severity of neurological deficit, APACHE II scores at the time of hospitalization, and the severity of most radiographic findings (Table 1). Differences between the study groups included a higher percentage of heavy smokers, diabetics, heavy alcohol users, and patients with cerebral edema on admission CT in the NRT group.

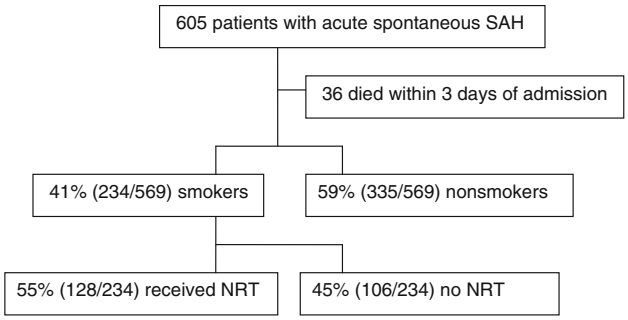

Fig. 1 Assignment of patients. *NRT* transdermal nicotine replacement therapy

Vascular complications, most notably symptomatic vasospasm and DCI (cerebral infarction or clinical deterioration due to vasospasm) occurred with equal frequency in the NRT and non-NRT groups (Table 2). There were no differences in the frequency of myocardial infarction, congestive heart failure, arrhythmia, and most other medical complications between the two groups. Smokers that did not receive NRT had lower than expected rates of pneumonia, pulmonary edema, fever, and seizures compared to both NRT-treated smokers and nonsmokers. Delirium was more common in the group receiving NRT.

Univariate analysis revealed several factors at the time of admission known to be associated with outcome: age, neurological status (Hunt and Hess grade, or GCS), radiographic findings (SAH Sum Score, cerebral edema, and aneurysm size), and APACHE II score. In this model, heavy smoking, pack-year history of tobacco use, and the chronological period of admission (before or after January 1, 2005) were not significant predictors of mortality, but NRT was associated with lower mortality (Table 3).

In our multivariable regression model, factors independently associated with death included age, cerebral edema on admission CT scan, poor neurological status at the time of hospital admission, and diffuse, thick clot in the subarachnoid space, reflected by a Hijdra (or SAH Sum Score) score >15. NRT in smokers remained strongly associated with survival, with a relative risk of death of 0.12 at a significance level of $P < 0.001$ (Table 4).

Discussion

This study was designed to evaluate the safety of transdermal nicotine replacement in a large cohort of active cigarette smokers with primarily aneurysmal SAH. NRT administered during the acute phase after SAH was not associated with clinical or radiographic vasospasm, or with

Table 1 Characteristics of the patients

	Non-smokers, n = 335	Smokers		P^a
		No NRT, n = 106	NRT, n = 128	
Demographics				
Age (years)	55 ± 15	50 ± 13	50 ± 12	0.84
Female	70 (231/331)	67 (71/106)	66 (85/128)	0.93
White	50 (167/335)	50 (53/106)	62 (79/128)	0.07
Lifetime pack years	4 ± 13	31 ± 34	34 ± 29	0.43
Heavy smoker[b]	N/A	47 (48/102)	73 (92/126)	<0.001
Heavy alcohol use	8 (24/297)	16 (15/96)	30 (36/118)	0.01
MI	2 (6/318)	6 (6/104)	1 (1/127)	0.03
CHF	2 (6/318)	2 (2/104)	2 (3/127)	0.82
Diabetes mellitus	9 (29/321)	2 (2/104)	11 (14/126)	0.006
Hypertension	49 (157/323)	38 (40/105)	43 (55/127)	0.42
Year of admission				
"Early" 2001–2004				
"Late" 2005–2007	46 (153/335)	31 (33/106)	55 (71/128)	<0.001
Clinical status on admission				
APACHE II subscore		10.7 (±7.8)	11.4 (±7.4)	0.49
Poor Grade Hunt-Hess [3–5]	54 (179/334)	54 (57/106)	54 (68/127)	0.97
Glasgow Coma Scale <8	19 (63/330)	20 (21/105)	20 (25/128)	0.93
Admission radiographic findings				
Hijdra SAH sum score ≥15	48 (152/319)	48 (49/103)	59 (71/121)	0.10
IVH present	51 (163/322)	51 (53/103)	54 (65/121)	0.74
Aneurysm size ≥10 mm	23 (63/273)	27 (24/88)	31 (36/118)	0.61
Cerebral edema	51 (165/324)	38 (40/106)	61 (78/127)	<0.001
ICH present	21 (36/168)	33 (20/61)	37 (25/67)	0.59

Values are percentages followed in parenthesis by absolute numbers, or mean values with the standard deviation in parenthesis

[a] *P* value reflects comparison of smokers with and without NRT

[b] >10 cigarettes/day

DCI, suggesting that exogenous NRT in smokers is unlikely to cause vasospasm. Delirium was more common in the patients receiving NRT—possibly because it was the indication for initiating therapy. Certain medical complications, such as seizures, pneumonia, and heart failure were more common among smokers receiving NRT, but rates were similar to those of nonsmokers. Three month mortality was lower in NRT-treated patients than in the smokers who did not receive NRT. Although these findings are of interest and warrant further investigation, the overall number of deaths was small, and lower in the NRT group than even in nonsmokers. This apparent mortality benefit could be due a neuroprotective property of nicotine, to an unrecognized confounder, or to chance.

We chose mortality as the primary endpoint, with DCI, angiographic, and TCD evidence of vasospasm as secondary endpoints, because of recent reports of increased mortality among critically-ill medical, surgical, and cardiac surgical patients receiving NRT [20, 22], Although the matching of study groups was imperfect, the major predictors of mortality after SAH: age, Hunt-Hess grade, aneurysm size, SAH sum score, and APACHE II sum score were similar in the two groups. The most important differences were that the NRT group included a higher percentage of heavy smokers and heavy alcohol users, and had a higher incidence of cerebral edema on presentation (a strong marker of the severity of ictus), while more smokers who did not receive nicotine had a history of MI.

Delirium was more common in the group receiving NRT, possibly related to the higher incidence of heavy alcohol use, and to the fact that delirium with nicotine withdrawal was the primary indication for NRT [6]. It is unlikely that NRT caused delirium, but this association warrants further study. Additionally, there were more frequent seizures in the NRT group—an association that could either be a side effect of the high dose of NRT employed (21 mg), or related to greater delirium and severity of ictus.

Table 2 Complications

	Nonsmokers, n = 335	Smokers, no NRT, n = 106	Smokers that received NRT, n = 128	P^a	OR[a]	CI[a]
Clinical vasospasm	22 (75/335)	23 (24/106)	25 (32/128)	0.60	1.18	(0.63–2.21)
Delayed cerebral ischemia	23 (75/330)	23 (24/106)	25 (32/127)	0.65	1.15	(0.63–2.11)
Rebleeding	9 (30/335)	7 (7/106)	6 (8/128)	0.912	0.94	(0.33–2.69)
Angiographic vasospasm	7 (23/320)	15 (15/101)	8 (10/120)	0.128	0.52	(0.22–1.22)
Vasospasm induced infarct	10 (32/335)	12 (13/106)	10 (13/128)	0.61	0.81	(0.36–1.83)
Pneumonia	29 (94/328)	17 (18/106)	29 (36/126)	0.037	1.96	(1.03–3.74)
Pulmonary edema	22 (74/332)	9 (10/106)	24 (30/126)	0.004	3.00	(1.40–6.44)
Myocardial infarction	8 (28/331)	9 (9/105)	4 (5/127)	0.14	0.44	(0.14–1.34)
Congestive heart failure	12 (39/332)	8 (8/106)	11 (14/127)	0.36	1.52	(0.62–3.74)
Delirium[b]	10 (34/332)	7 (7/106)	19 (24/127)	0.006	3.30	(1.37–7.97)
Fever	56 (184/329)	47 (50/106)	59 (74/125)	0.068	1.63	(0.96–2.77)
Seizures	8 (28/331)	2 (2/106)	9 (11/126)	0.024	4.97	(1.08–2.92)
Arrhythmia	12 (39/332)	7 (7/106)	10 (12/126)	0.42	1.49	(0.56–3.97)
Hyperglycemia	56 (186/332)	50 (53/106)	60 (75/126)	0.15	1.47	(0.87–2.50)
Hypernatremia	27 (90/332)	28 (30/106)	29 (36/126)	0.96	1.01	(0.57–1.78)
Hyponatremia	14 (47/332)	15 (15/106)	20 (25/126)	0.35	1.39	(0.70–2.76)
Anemia	42 (138/332)	41 (43/106)	38 (48/127)	0.67	0.89	(0.52–1.51)
Hypotension	26 (86/332)	32 (34/106)	26 (33/127)	0.31	0.74	(0.42–1.31)
Death at 3 months	16 (55/334)	17 (18/106)	7 (9/128)	0.02	0.37	(0.16–0.86)

Figures are %, followed by absolute number

NRT nicotine replacement therapy

[a] *P*-value, OR and CI reflect smokers with and without NRT; nonsmokers are shown for comparison

[b] See text for clinical definition of delirium

Table 3 Factors associated with death among active smokers with SAH: univariate analysis

Factor	Alive n = 207	Dead n = 27	OR	*P*
Age (mean)	57 ± 16	49 ± 12		0.003
Heavy smoking	60 (122/203)	72 (18/25)	1.71	0.249
Hunt-Hess grade 3–5	50 (102/206)	85 (23/27)	5.86	<0.001
Admission GCS <8	15 (30/206)	59 (16/27)	8.53	<0.001
Pack year history smoking[a]	24 (11, 42)	45 (24,55)		0.006
Hijdra SAH sum score ≥15	50 (100/199)	80 (20/25)	3.96	0.005
Cerebral edema	46 (95/206)	85 (23/27)	6.72	<0.001
Apache II subscore	19 ± 8	10 ± 7		<0.001
Aneurysm size >10 mm	27 (49/184)	50 (11/22)	2.76	0.023
2001–2004 (earlier) admission	45 (94/207)	37 (10/27)	1.41	0.41
History of MI	2 (4/205)	12 (3/26)	6.55	0.007
Nicotine replacement therapy	57 (119/207)	33 (9/27)	0.37	0.018

Values are mean ± SD or % (N)

[a] Presented as Median (IQR)

Smokers receiving NRT had lower mortality when compared to smokers without NRT, but also to nonsmokers. Although the overall number of deaths was small, and therefore vulnerable to random effects, improved mortality among smokers receiving NRT could reflect a salutary effect of NRT in the injured brain following SAH. Such a benefit might be due to attenuation of a previously underrecognized nicotine withdrawal syndrome, to a fundamental neuroprotective property of nicotine, or to the increased susceptibility of neurons to injury during nicotine

Table 4 Factors associated with death among active smokers with SAH: multivariate analysis

Factors associated with death in SAH in multivariable model	OR	CI	*P*
Age	1.07	1.02–1.11	0.005
Cerebral edema	9.61	2.26–40.84	0.002
SAH sum score >15	3.5	1.06–11.58	0.04
Admission Hunt and Hess Grade	1.72	1.12–2.64	0.014
Nicotine replacement therapy	0.12	0.04–0.39	<0.001

withdrawal. Considering the retrospective design of the study, an alternate explanation for the mortality difference is a confounding unrecognized variable. For example, we were unable to determine why patients did or did not receive nicotine, but one likely explanation is that certain clinicians preferred treatment, therefore introducing a caregiver bias between the groups. It is also true that the routine care of SAH evolved over the time period of the study, and more smokers received nicotine during the later study period—a second source of bias that could favor survival in patients receiving nicotine.

Although suppression of a nicotine withdrawal syndrome might explain the apparent higher survival with NRT, the SHOP database rigorously tracks medical complications, and the non-NRT group did not suffer more heart failure, MI, pulmonary edema, pneumonia, fever, renal failure, hyperglycemia, sodium disturbances, or any other obvious medical complication to suggest a systemic drug withdrawal syndrome. Nor, as some authors have suggested, was NRT associated with a greater risk of infections [35]. Unfortunately, since many patients probably received nicotine in response to delirium, we cannot evaluate that association.

It is interesting to postulate a neuroprotective role for nicotine in acute brain injury. Nicotine's effects on nicotinic acetylcholine receptors and regional blood flow in the brain are complex, important, and incompletely understood. Chronic exposure is known to change the structural plasticity of the brain [36, 37]. Nicotinic receptor activation acutely causes the release of dopamine, glutamate, norepinephrine, acetylcholine, serotonin, B-endorphin, and gamma-aminobutyric acid (GABA), and acute smoking cessation causes a state of "subnormal release of dopamine and other neurotransmitters [38]." Non-smokers develop Parkinson's Disease at twice the frequency of smokers [39–41]. Animal studies show that cigarette smoke protects against MPTP-induced neurotoxicity in the dopaminergic nigrostriatal system, possibly by protecting neurons against oxidative damage caused by the metabolism of dopamine [42–44]. Nicotine has been shown in neuronal cultures to offer protection against neurotransmitter-related excitotoxicity [45, 46], and against arachadonic acid [47]. In an in vitro and in vivo model, nicotine pretreatment was neuroprotective in dopaminergic cells against inflammation caused by the lipopolysaccharide induced activation of microglia [48].

Our modest preliminary data support the safety of NRT in smokers hospitalized with acute SAH. NRT was not clearly effective at reducing delirium, however, and given an increased incidence of seizures, should be used only with caution until prospective data are available, perhaps limited to heavy smokers. Bench research and preliminary human trials should prospectively evaluate the safety and efficacy of NRT at preventing delirium and nicotine withdrawal in smokers with acute SAH, and should consider the possibility of a neuroprotective effect of nicotine in the injured brain.

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