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Review article

Nicotine replacement therapy in patients with aneurysmal subarachnoid hemorrhage: Systematic review of the literature, and survey of Canadian practice

Ricky D. Turgeon [a,*], Stephano J. Chang [b], Charlotte Dandurand [b], Peter A. Gooderham [b], Camille Hunt [b]

[a] Department of Medicine (Division of Cardiology), University of Alberta, 116 St & 85 Ave, Edmonton, AB T6G 2R3, Canada
[b] Division of Neurosurgery, Vancouver General Hospital, 899 West 12th Avenue, Vancouver, BC V5Z 1M9, Canada

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ABSTRACT

Tobacco smoke increases the risk of aneurysmal subarachnoid hemorrhage (SAH), as well as complications such as vasospasm. Most patients presenting with aneurysmal SAH smoke, and many survivors continue to smoke after discharge. Neurosurgeons often hesitate to use nicotine replacement therapy (NRT) during hospitalization of patients with SAH due to concerns of inducing vasospasm. We aimed to evaluate the safety and efficacy, and patterns of use of NRT in smokers hospitalized for SAH. We performed a systematic review of MEDLINE, CENTRAL, Embase, and unpublished sources of literature to October 2016 for randomized and observational studies comparing exposure to non-exposure of smoking cessation products in the acute phase of aneurysmal SAH. Additionally, we surveyed 50 Canadian vascular neurosurgeons to evaluate patterns of NRT use in SAH. Four cohort studies ($n = 1210$) met our eligibility criteria. Three studies enrolled patients with aneurysmal SAH, and one study enrolled all neurocritically ill patients. We rated the quality of evidence as very low using the GRADE approach. We could not meta-analyze studies due to methodological heterogeneity. Individual studies reported beneficial or neutral effects of NRT on functional outcome, death, and clinical or radiographic vasospasm. None of the studies assessed long-term abstinence from tobacco. Of the 14 vascular neurosurgeons responding to our survey, most never used NRT in patients hospitalized with SAH, often citing training or standard of practice as the reason. Current evidence suggests that NRT does not induce vasospasm, and is associated with improved outcomes in smokers hospitalized for SAH.

Protocol registered in PROSPERO, available at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016037200.

1. Introduction

Aneurysmal subarachnoid hemorrhage (SAH) occurs in approximately 10 per 100,000 individuals per year [1]. Smoking tobacco is an important risk factor for aneurysm growth and rupture, and more than doubles the risk of aneurysmal SAH [2–4]. As a result, 50–66% of patients with aneurysmal SAH are active smokers, which increases the risk of in-hospital complications, including vasospasm and delayed cerebral ischemia (DCI) [2,5–7]. Furthermore, greater than one-third of smokers who survive aneurysmal SAH continue to smoke after discharge [8].

No consensus or guideline recommendations exist on the management of tobacco dependence in patients hospitalized for aneurysmal SAH [9,10]. Some neurosurgeons avoid nicotine replacement therapy (NRT) in the acute phase due to the negative impact on outcomes associated with tobacco smoke. However, animal models suggest that these associations may be unrelated to nicotine, instead caused by the numerous other toxins present in tobacco smoke [11,12]. Conversely, neurosurgeons at other centers routinely initiate NRT in all of their SAH patients who smoke [8]. In the short-term, the main consequence of withholding NRT is nicotine withdrawal, which can increase patient discomfort and anxiety, and in some cases leads to delirium [13]. Additionally, multiple trials in various disease states demonstrate lower rates of long-term smoking abstinence when smoking cessation therapies are withheld during hospitalization [14].

We performed a systematic review of randomized and controlled observational studies evaluating the impact of NRT and other pharmacological smoking cessation agents on clinical

* Corresponding author at: 301-2504 109 St NW, Edmonton, AB T6J2H3, Canada.
E-mail address: rturgeon@ualberta.ca (R.D. Turgeon).

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outcomes in patients hospitalized with aneurysmal SAH. Additionally, we surveyed Canadian vascular neurosurgeons to identify patterns of practice regarding use of nicotine replacement therapy in smokers hospitalized for aneurysmal SAH.

2. Material and methods

2.1. Systematic review

2.1.1. Study selection and search strategies

We performed this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement, and registered our protocol on PROSPERO prior to data analysis and interpretation (available online at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016037200) [15]. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), Embase and MEDLINE from database inception to October 13, 2016 for relevant articles using the following search terms: *subarachnoid hemorrhage* or *ruptured aneurysm,* and *smoking cessation, nicotine, bupropion, clonidine, notriptyline* or *varenicline*. For gray, unpublished and ongoing literature, we searched the World Health Organization International Clinical Trials Registry Platform and ClinicalTrials.gov, and performed a manual search of bibliographies of included studies and relevant reviews. Three reviewers (SC, CD, RT) independently screened titles, abstracts, and full-text articles for eligibility for our review. We resolved any discrepancies by consensus.

We included all randomized controlled trials (RCTs), cohort and case-control studies published in any language that evaluated medications for smoking cessation in patients in the acute phase of aneurysmal SAH (i.e. in hospital during the first 21 days from symptom onset).

2.1.2. Data extraction and quality assessment

One reviewer (RT) extracted all data using a standardized collection form, and 2 reviewers (SC and CD) audited the data. We extracted the following data whenever available: Full citation, study methodology (setting, timeframe, country) number of study participants in each group, baseline characteristics (aneurysmal SAH diagnostic criteria, clinical and radiographic grade, presence/absence of hydrocephalus), aneurysm characteristics (location, size and number), method of aneurysm obliteration (surgical clipping versus endovascular coiling), co-interventions (ventriculostomy for hydrocephalus, nimodipine, statins, hemodynamic therapy), intervention details (drug, dose, formulation, time started from aneurysmal SAH onset, duration of therapy), and outcome definitions. We extracted the following pre-defined outcomes of interest: Functional outcome (our primary outcome; as determine by modified Rankin Score [mRS], Glasgow Outcome Score [GOS] or expanded GOS at latest follow-up); death; clinical vasospasm or delayed cerebral ischemia; radiographic vasospasm; delirium; length of stay (LOS) in hospital or intensive care unit (ICU); and abstinence from tobacco post-discharge.

We rated study quality based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [16]. Briefly, we classified overall study quality for each trial as very low, low, moderate or high based on study design (randomized or observational), risk of bias, consistency, directness, and precision.

2.2. Survey

We surveyed all known Canadian vascular neurosurgeons regarding their use of nicotine replacement therapy in patients hospitalized with aneurysmal SAH. We obtained approval to perform this survey from the University of British Columbia (UBC) Ethics Review Board. We sent e-mail invitations to eligible participants with a link to a secure online survey on August 7 2016, followed by two reminder e-mails over 6 weeks.

3. Results

We included four of 284 identified articles, including three full-text articles and one study available only in abstract form evaluating the use of NRT in patients with aneurysmal SAH (Fig. 1). We did not identify any study assessing non-NRT pharmacological agents for smoking cessation in SAH. Table 1 lists methodological and clinical characteristics of the included studies. Because all included studies were observational and suffered from imprecision, we graded the quality of the body of evidence as very low based on the GRADE approach. We judged the included studies to be too methodologically and clinically heterogeneous to meta-analyze. We therefore summarize the results of the included studies narratively and present data on our pre-defined outcomes in Table 2.

All four articles reported cohort studies using retrospectively-collected medical records data. Three of the studies enrolled patients with aneurysmal SAH [17–19], whereas one evaluated all patients in their neurocritical care unit, including patients with aneurysmal SAH [20]. In the three full-text articles [17,18,20], investigators administered NRT as a transdermal patch, generally administered until discharge. In two of these studies [18,20], the dose was a fixed 21 mg daily, whereas the third study administered 7 to 21 mg daily at the discretion of the prescribing physician [17]. Rowe et al. did not report the dose or formulation of NRT [19].

3.1. Functional outcome

Three studies reported functional outcome at discharge using different outcome definitions [17,19,20]. No study evaluated longer-term functional outcome. Overall, one study demonstrated a statistically significant association between NRT use in smokers and better functional outcome [17], and two studies reported no statistically significance difference, but could not exclude clinically relevant benefit or harm of NRT [19,20].

Carandang et al. reported the proportion of patients achieving good outcome on discharge, defined as Glasgow Outcome Score

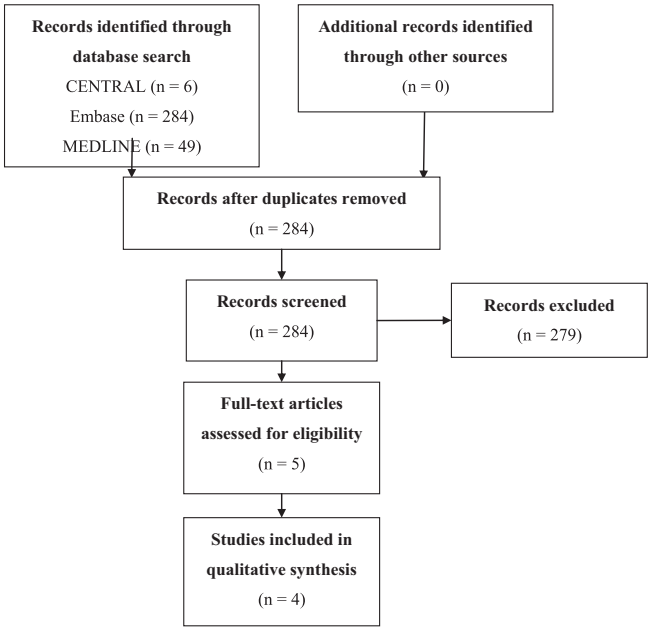

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram of clinical studies.