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Safety of nicotine replacement therapy in critically ill smokers: a retrospective cohort study

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Abstract *Purpose:* Nicotine replacement therapy (NRT) has been used to ameliorate nicotine withdrawal in the intensive care unit (ICU). Previous cohort studies have suggested an increased mortality with NRT use: methodological problems may call into question the validity of these findings. We undertook a retrospective cohort study to determine if NRT use was associated with adverse outcomes. *Methods:* This retrospective cohort study was conducted in a 30-bed, university affiliated, teaching hospital ICU. *Results:* We identified 423 smokers admitted over 2 years, of whom 73 received transdermal NRT. Cox proportional hazard regression models, with NRT modelled as a time-varying covariate, were used to test the hypothesis that NRT was associated with an altered ICU or hospital mortality. A second analysis utilized propensity scores. The unadjusted ICU and hospital mortalities were lower for the NRT group; although both differences were non-significant. The Cox models showed that, after adjustment for APACHE risk, age, sex and alcohol use, risk associated with NRT administration was not statistically different than non-administration for both ICU (hazard ratio 0.50, [95 % CI 0.20–1.24], $p = 0.14$) and hospital (hazard ratio 0.95, [95 % CI 0.52–1.75], $p = 0.88$) mortality. Similar findings occurred with the propensity matched analysis. *Conclusion:* We were unable to demonstrate any harm associated with NRT, with the ICU model actually trending towards benefit. We conclude that a randomised, blinded, placebo controlled trial is required to assess adequately the safety and efficacy of NRT as a treatment in critically ill smokers.

Keywords Intensive care · Nicotine · Smoking · Delirium · Cohort study

Introduction

Tobacco, particularly as cigarette smoking, remains a leading cause of preventable death in developed countries [1]. Although the prevalence of smoking has declined steadily over the last three decades, 22 % of the UK's adult male population reported themselves as smokers in 2007 [2]. Smokers manifest a higher incidence of lung and other malignancies and are also at increased risk of other cardio-respiratory conditions including chronic obstructive pulmonary disease and ischaemic heart disease (IHD), which may necessitate or complicate an admission to the intensive care unit (ICU).

Nicotine replacement therapy (NRT) which can be delivered by a variety of methods (chewing gum, transdermal patches, nasal spray, inhalers, tablets, electronic cigarettes and lozenges) has originally been advocated as a means to aid transition to complete abstinence from

cigarette smoking; there is strong evidence that NRT reduces motivation to smoke and may alleviate withdrawal symptoms [3].

Agitation and delirium are common in the critically ill population [4] and are associated with adverse outcomes [5], although causality is not established. Nicotine withdrawal has been identified as a contributing factor to this [6]. Hence NRT may, by mitigating the effects of nicotine withdrawal, improve ICU outcome. Data to support the use of NRT in the ICU population are sparse; two recent studies have, surprisingly, shown potential harm with NRT. In 2007 Lee and Afessa [7] published a retrospective case–control study of 90 smokers treated with NRT on the ICU and concluded that the treatment was associated with significantly increased hospital mortality. The cause for this was unclear; the authors postulated that potential reasons may have included sympathomimetic cardiovascular effects of nicotine in the setting of reduced oxygen delivery and highlighted the lack of safety data for NRT in the critically ill, despite several trials demonstrating the safety of NRT in patients with IHD [8, 9]. In the critical care setting Paciullo and co-workers [10] described an increase in hospital mortality associated with NRT in a retrospective study of 134 patients who had undergone coronary artery bypass grafting (CABG).

Interestingly, a further prospective observational cohort study undertaken by Cartin-Ceba et al. [11] in the same institution as Lee and Afessa and published 4 years later failed to reproduce these findings.

St Thomas' Hospital is a university affiliated teaching hospital with a 30-bed mixed medical and surgical ICU. The hospital provides tertiary and quaternary services to London and the South East of England. The ICU is a closed unit, staffed by intensivists with 1:1 nurse to patient ratios. Prior to 2007 NRT was prescribed in our ICU. This practice was questioned following publication of Lee's [7] paper due to concerns regarding potential patient harm. We thus undertook a retrospective study using a cohort of smokers at St Thomas' Hospital and using robust statistical methodology. First, all smokers were included. Second, we adjusted for the fact that NRT may be instituted at varying times after ICU admission by including this as a time-varying covariate, thereby adjusting for potential immortal time bias [12].

Finally we undertook an alternative analysis using matching based upon a propensity score. Our primary hypothesis was that, after adjustment for important covariates, NRT would be associated with an altered hazard for both ICU and hospital mortality.

Methods

A local research ethics committee reviewed the proposed study and waived the need for full ethical submission, as the study met the national criteria for service evaluation. The study was thus registered as an audit as per institutional guidelines (St Thomas' Hospital Research Ethics Committee Reference 07/022).

Data were collected retrospectively on all patients who were categorised as current smokers admitted to the ICU between 1 January 2005 and 31 December 2006. Smokers were identified via screening the admission fields of our electronic patient records (ICIP, Philips, UK) for terms relating to smoking history. Other extracted data included admission diagnosis, age, sex, APACHE II, prescription of NRT, alcohol intake of greater than 21 units per week, new prescription of drugs for agitation or delirium (benzodiazepines, haloperidol or clonidine) during ICU admission and hospital and ICU length of stay and mortality. New prescription of two or more anti-agitation drugs and a validated chart review confirming the presence of an acute confusional state was used as a surrogate for agitation or delirium. Validated chart review with prescription of two or more anti-agitation drugs has previously been used as a tool for identification of agitation and/or hyperactive/mixed delirium in the ICU setting both in our institution [13] and elsewhere [14].

Statistical analysis

Data were analysed using STATA v11 (Statcorp, TX, USA). Bivariate comparisons included Student's t tests, Mann–Whitney U and Fisher's exact tests as appropriate. Cox proportional hazards regression was used to test the hypothesis that NRT use was associated with a change in ICU or hospital mortality risk over time. Potential confounders included age, APACHE II score, gender, and history of significant alcohol use. The co-primary end points were ICU and hospital mortality. Because NRT could be started after ICU admission, with potential for self-selecting survivors (so-called immortal time bias), NRT was entered as a discrete time-varying covariate [12]. Post estimation tests of the Cox models included checking the following: (a) proportionality assumption with log(−log) survival probability versus log-time plots, and scaled Schoenfeld residuals versus time plots, (b) model fit with scaled deviance residuals versus linear predictor plots, and (c) influential points via dfitbetas and log-likelihood displacement plots.

We also tested the same hypotheses using a matched analysis based upon a propensity score. The same variables, plus addition of admission category (surgical versus medical) were used for construction of the propensity score (outcome variable was the use of NRT). Matching was 1:1, and was based upon the logit of the propensity score, using $5 \rightarrow 1$ digit matching, as suggested by Austin [15]. Balance of covariates between the NRT and control groups was assessed using the standardised difference, with values less than 0.25 being desirable for a

sample size of 75 matched pairs [16]. Comparison of matched pairs was then undertaken using univariable logistic regression (NRT vs. control) estimated via generalised estimating equations to account for the matching [17].

In all cases, a p value of greater than 0.05 was considered significant.

Results

We identified 423 smokers admitted to the ICU over the 2-year period, of whom 73 received transdermal NRT (Table 1). Complete records were available for all cases. The critical care unit at St Thomas' Hospital admits approximately 1,200 patients per year so 423 smokers was thought to be a likely representative of the true number (ca. 18 %). NRT was instituted at a median (IQR) time of 2.3 (1.5–5.0) days post ICU admission, at a median dose of 20 mg/day (range 10–30 mg). Therapy was given for a median duration of 6 days (IQR 3–9 days). NRT was prescribed on a case by case basis at the discretion of the treating physician; however because a higher proportion of NRT patients required two or more anti-agitation agents (26 % compared with 7 % in the non-NRT group, $p < 0.001$), it suggested that agitation may have been a key factor in prescribing NRT.

The unadjusted ICU and hospital mortalities were not significantly different between groups. Nonetheless, the lower mortality rates and lower APACHE mortality risk seen in the NRT group and the timing of commencement of NRT may suggest immortal time bias (NRT patients only received this therapy if they lived long enough for agitation to become apparent), underlining the need to include NRT as a time-varying covariate and adjust for disease severity in the multivariable analyses. Unsurprisingly, the NRT group also had a higher incidence of heavy alcohol use; the remaining demographic variables did not differ between the two groups. The unadjusted length of stay for ICU survivors in the NRT group was almost double that of the non-NRT group (16 vs. 9 days, $p = 0.001$); however this difference did not persist for hospital stay (35 vs. 34 days, $p = 0.56$).

The Cox models (Table 2; Fig. 1) showed that, after adjustment for APACHE risk, age, sex and alcohol use, the hazard ratios for NRT administration were not statistically significant for both ICU and hospital mortality. Diagnostic checks revealed no problems with model misspecification, nor influential outliers.

Similar results were seen for the propensity score matched, logistic regression analyses (73 matched pairs). The odds ratio (95 % CI) for the NRT group was 0.50 (0.19–1.33, $p = 0.17$) for ICU death, and 0.54 (0.25–1.13, $p = 0.10$) for hospital death. The baseline covariates were well balanced between the matched groups, with standardised differences ranging from 0.014 (gender) to 0.151 (age).

Discussion

The rationale for NRT in critically ill smokers represents a balance between potential risk and benefit. Delirium is associated with adverse outcomes, both in the ICU and in the post discharge period [5] and nicotine withdrawal may

Table 1 Demographic and unadjusted outcome data

	NRT ($n = 73$)	Control ($n = 350$)	p
Age	55.5 (13.9)	56.3 (16.9)	0.70
Male sex	64.9 %	67.4 %	0.69
Alcohol >21 units/week	50 %	21.7 %	<0.001
APACHE II mortality risk	21.8 (15.5)	27.2 (20.1)	0.06
>2 sedative agents	25.7 %	7.1 %	<0.001
Survivor length of ICU stay	15.7 (19.7)	9.0 (13.8)	0.001
Survivor length of hosp stay	34.6 (52.7)	33.8 (52.8)	0.56
ICU mortality	8.1 %	15.1 %	0.14
Hospital mortality	17.6 %	23.4 %	0.36
Specialty			0.01
All medical	45 (61.6 %)	267 (76.3 %)	
Cardiology	3 (4.1 %)	60 (17.1 %)	
Respiratory	19 (26.0 %)	89 (25.4 %)	
Gastroenterology	4 (5.5 %)	14 (4.0 %)	
Neurology	2 (2.7 %)	24 (6.9 %)	
General medicine	14 (19.2 %)	54 (15.4 %)	
Oncology	0	1 (0.3 %)	
Renal	3 (4.1 %)	25 (7.1 %)	
All surgical	28 (38.4 %)	83 (23.7 %)	
Trauma/orthopaedics	6 (8.2 %)	9 (2.6 %)	
Vascular	1 (1.4 %)	25 (7.1 %)	
General surgery	15 (20.6 %)	28 (8.0 %)	
Cardiothoracic surgery	6 (8.2 %)	21 (6 %)	

Table 2 Cox proportional hazards models (NRT included as a discrete time-varying covariate)

	Hazard ratio	95 % CI	*p*
Model 1: ICU mortality			
NRT	0.50	0.20–1.24	0.14
Sex (male)	0.95	0.56–1.62	0.85
Age (per year)	1.01	0.99–1.03	0.17
Alcohol >21 units/week	0.99	0.54–1.83	0.99
APACHE II risk (per 1 % increase)	1.03	1.02–1.04	<0.001
Model 2: hospital mortality			
NRT	0.95	0.52–1.75	0.88
Sex (male)	1.10	0.71–1.70	0.66
Age (per year)	1.03	1.01–1.04	0.001
Alcohol >21 units/week	1.11	0.69–1.80	0.66
APACHE II risk (per 1 % increase)	1.03	1.02–1.04	<0.001

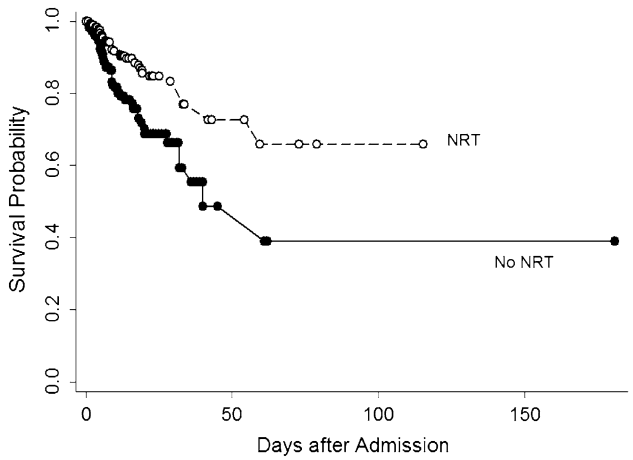

Fig. 1 Kaplan–Meier curve of NRT vs. no NRT

contribute to this. A summary of studies investigating the use of NRT in the critical care setting is outlined in Table 3.

Lucidarme et al. [18] undertook a prospective study of 144 consecutive admissions to two French ICUs of whom 44 patients were smokers. The smokers in this study were more likely to have a history of alcohol use and had a higher incidence of agitation, but the incidence of delirium using the Intensive Care Delirium Screening Checklist (ICDSC) was similar in both groups. Nicotine withdrawal was associated with higher incidence of self-removal of tubes and catheters, and with increased requirement for sedation and physical restraint.

Lee and Afessa's study of 2007, also a retrospective study, had methodological differences to ours. In their study 90 critically ill smokers who had received NRT over a 4-year period were matched with 90 critically ill smokers admitted over the same period. The control patients were selected by the investigators on the basis of APACHE III score, age and "similarity to the case". Several methodological aspects of Lee's study may call into question the validity of their findings. The sample size was small (180 cases from 6,735 admissions), aspects of the matching procedure were unclear and 22 % of NRT patients were excluded for a variety of reasons. This may have introduced bias and may explain the significant association with hospital mortality ($p = 0.0085$) [7].

The study undertaken by Paciullo et al. [10] used a similar methodology; 67 patients undergoing CABG who received NRT on the ICU were matched by the investigators to 67 smokers undergoing similar procedures who did not receive NRT.

Despite the strong signal to harm seen in Lee and Afessa's original study a prospective cohort study was subsequently undertaken at the same institution by Cartin-Ciba et al. Because NRT continued to be offered to all smokers at this institution, the control group of this second study consisted of those patients where NRT was refused by patients or their next of kin, known allergy to NRT patches or pregnancy. This approach was again likely to be subject to bias. In this study the control group was significantly more likely to smoke less, have coronary heart disease or not be ventilated and there was no demonstrable difference in any of the primary outcome measures used: ICU and hospital mortality, ICU and ventilator-free days. There was however increased incidence of delirium measured by the Confusion Assessment Method for ICU (CAM-ICU) in the NRT group. The NRT group was also more likely to be physically restrained, received higher doses of benzodiazepines or opioids. Unfortunately data on alcohol consumption was not collected in this study and as the authors point out there is a strong association with alcohol and smoking, so this may have further confounded the findings.

Table 3 Summary of studies investigating NRT use in critically ill adults

Study	Population	*n*	Design	Main findings
Mayer et al. [6]	Neuro-ICU patients	5	Case series	Improvement in delirium with administration of NRT
Lee and Afessa [7]	Medical ICU	180	Retrospective, case control	Increased mortality in NRT treated group
Paciullo et al. [10]	Cardiothoracic ICU	134	Retrospective, case control	Increased mortality in NRT treated group
Cartin-Ceba et al. [11]	Medical ICU	330	Prospective cohort study	No significant differences between groups
Current study	Mixed medical/ surgical ICU	423	Retrospective cohort study	No significant differences between groups

In contrast to the studies outlined above, after adjustment for important confounders, we failed to demonstrate a difference in ICU or hospital mortality among smokers who received NRT. We screened and included all smokers, rather than matching 1:1 thereby increasing sample size and decreasing the likelihood of selection bias. We included NRT as a time-varying covariate, to avoid immortal time bias. This meant that patients who subsequently received NRT were counted as controls up until the time that they received the drug, at which point they crossed over into the NRT group. In our study the hazard ratios for NRT were very close to 1 (0.50 for ICU and 0.95 for hospital mortality, respectively) suggesting NRT was not associated with increased harm. Moreover the events per variable ratio in the multivariable models was greater than 10 (i.e. 59 ICU deaths and 5 variables screened) which minimises the potential for overfitting (i.e. formulating a model that is unduly influenced by idiosyncrasies in your own data).

Our study has several important limitations. Firstly it is a retrospective cohort study from a single institution. This raises the possibility of selection bias. However, our unit is a large, tertiary ICU which covers all major specialties with the exception of neurosurgery and hepatology. We obtained complete records on all smokers identified by our electronic database; hence the main potential for the selection bias may have been data entry errors in terms of identifying smokers. We suspect the likelihood of this is small, and any error will likely be non-systematic.

Second, and of far more importance, is the potential for treatment selection bias, as NRT prescribing was at the discretion of the responsible ICU consultant. Here bias could be for a variety of reasons such as confounding by indication [19], or perhaps competing medical issues [20]. For example, patients may have preferentially been prescribed NRT when the clinician felt that they were "stable enough" i.e. clinicians may have inadvertently selected those for NRT who were likely to survive. This type of bias will not be eliminated by addition of treatment as a time-varying covariate.

We considered whether the potential for treatment selection bias could have been reduced via alternative analyses, using matching by propensity score. These yielded very similar results to the Cox models; however this is not surprising given that similar covariates were used for both analyses, and is also consistent with other studies when both types of analyses have been used on the same data set [21]. Simulation studies have shown that propensity matching offers little advantage over standard multivariable methods when the ratio of events to covariates is greater than 8, as is the case in our study [22]. In addition, propensity matching will not adjust for unknown important confounders [23], and underlines the need for a randomized controlled trial.

Finally, we did not use CAM-ICU or ICDSC to diagnose acute agitation or delirium although these scoring systems are not used in our institution or widely throughout the UK [24]. Instead the prescription of anti-agitation agents was used as a marker for agitation and/or hyperactive/mixed delirium, the presence of which was then confirmed utilizing a validated chart review. This method was first described by Pisani and colleagues in 2006 [14] and the sensitivity and specificity of this method for diagnosing ICU delirium are quoted as 64 % and 85 % respectively [25].

Conclusion

We were unable to demonstrate any harm associated with NRT in our institution, neither are we able to recommend NRT on the basis of beneficial effects on length of stay or reduction in requirement of treatment for agitation. Our study findings are at odds with the original study undertaken by Lee and Afessa and concordant with the later study carried out at the same institution, although we believe our statistical approach is more appropriate than that taken by either of these studies. Had our study shown harm, then this may preclude a properly conducted prospective study.

We conclude that equipoise exists for a randomised, blinded, placebo controlled trial to assess the safety and benefits of NRT as a treatment in critically ill smokers.

Conflicts of interest None declared.

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