

Outcome of Nicotine Replacement Therapy in Patients Admitted to Intensive Care Unit: a Randomized Controlled Double-Blind Prospective Pilot Study.

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Author Contributions: Designed research study, performed data collection/analysis/interpretation, literature review, wrote the paper, review/edit/final approval of the paper, takes full responsibility for the paper: VP

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Word count: 264 abstract; 2289 text; 3 tables; 19 references

Running header: Nicotine replacement therapy in ICU patients

Conflict of Interest Statement: There are no real or potential conflicts of interest on the part of any author.

Randomized Trial Statement: This has been registered with the International Standard Randomised Controlled Trial Number (ISRCTN). The ISRCTN Register complies with requirements set out by the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the International Committee of Medical Journal Editors (ICMJE) guidelines, and complies with the WHO 20-item Trial Registration Data Set.

Abstract

Introduction: The effect of nicotine withdrawal in smokers admitted to intensive care units (ICUs) is not well understood; therefore, the role of nicotine replacement therapy (NRT) in those patients is controversial.

Objective: To demonstrate that NRT in ICU patients decreases need for sedatives/analgesics, number of days on ventilator, and total length of ICU stay.

Methods: The study was performed in a 20-bed ICU. Forty patients meeting inclusion/exclusion criteria were randomized into either an interventional or control group. Patients in the interventional group received a 21mg nicotine patch daily until either discharged from the ICU, transferred to a medical floor, or after 10 weeks. Patients in the control group received a placebo (no drug) patch. Use of sedatives/analgesics during ICU stay and use and duration of mechanical ventilator were collected. Length of ICU stay was compared between groups.

Results: There were 27 male and 13 female patients. Mean age was 57.4 years in the interventional group and 52.5 years in the control group. Mean APACHE II score was 14.3 in the interventional group versus 13.8 in the control group. Mean length of ICU stay was 4.5 days in the interventional group, compared to 7 days in the control group. Mean number of days on ventilator was 1.9 in the interventional group versus 3.5 in the control group. Number of days on sedation/analgesia was less in the interventional group compared to the control group.

Conclusion: Although the length of ICU stay and number of days on ventilator seemed to decrease numerically in this pilot study, statistically there was no beneficial effect demonstrated in patients receiving NRT.

Key words: Intensive care unit; nicotine addiction; nicotine replacement therapy; smoking status

Introduction

There is vast literature establishing nicotine addiction in people who smoke, and when smokers are admitted to intensive care units (ICU), they must cope with the effects of enforced nicotine withdrawal.^{1,2} The effects of nicotine withdrawal in smokers admitted to the ICU are not well understood.² There is limited available data that addresses the use of nicotine replacement therapy (NRT) in hospitalized smokers;³ therefore, the role of NRT in smokers admitted to ICUs remains controversial.⁴ We conducted a placebo-controlled, double-blind, randomized, prospective study to demonstrate that NRT in ICU patients decreases the effects of nicotine withdrawal, thereby, decreasing the use of sedatives and analgesics, number of days on ventilator, and total length of ICU stay. We herein report the preliminary results of our pilot study. We expect to complete the study over the course of the next few years, and at that time, we will report the complete study results.

Materials and Methods

Study design and subjects: This was a placebo-controlled, double-blind, randomized, pilot study done at St. Barnabas Hospital in Bronx, New York, in a 20-bed mixed medical/surgical ICU. Following approval by their Institutional Review Board, 40 patients were enrolled (20 in the interventional group, 20 in the control group). Patients who smoked more than 1 pack-per-day (PPD), with no contraindication to nicotine use, who met other inclusion and exclusion criteria (Table 1) were enrolled into the study. After providing informed consent, they were randomized into either the interventional (NRT) or control (placebo) group. Patients in the interventional group had a 21mg nicotine patch applied to the skin within 24 to 48 hours of ICU admission. A new patch was applied daily until either discharge from the ICU, transfer to a general medical

floor, or until 10 weeks had passed (if the patient was in the ICU for 10 weeks or longer, the weaning of nicotine was same as in outpatient settings over 10 weeks). Patients in the control arm had a “sham” (no nicotine) patch applied with the same frequency and duration. Patients and their care providers were unaware of which type of patch they received.

Data Collection: Intake data regarding cigarette smoking, co-morbidities, and reason for ICU admission were collected upon enrollment. Worst daily mean arterial pressures, heart rate, use of vasopressors, sedatives, and analgesics during ICU stay were collected after the application of each patch. Use and duration of mechanical ventilation was also collected, as was the total length of ICU stay. Investigators collecting the data were blinded as to whether the patient had a nicotine patch or placebo. Patients were followed only through their ICU stay.

Statistical Analysis: This study included 20 patients who had received NRT (i.e., the treatment group) and another 20 patients who had received the placebo (“sham”) treatment (i.e., the control group). The individual’s APACHE II (Acute Physiology and Chronic Health Evaluation) score was used as a matching variable between the treatment group and the control group. Discrete clinical characteristics (e.g., history of acquired immunodeficiency syndrome, coronary artery disease, and cancers) were compared between the treatment group and the control group using the McNemar’s test for paired data. Continuous clinical characteristics (e.g., the length of ICU stay in days, the number of packs of cigarettes smoked per day, and the number of days on sedation) were compared between the two groups using the Wilcoxon signed-rank test for paired data. Results were presented as the frequency, percentage, and *p*-value for discrete variables, and the mean, standard deviation, median, and *p*-value for continuous variables. A *p*-value of <0.05

was used to indicate statistical significance. All of the statistical analyses were carried out using a commercially available statistical software package (SAS).

Results

A total of 40 patients (20 interventional, 20 control) were followed over a 6-month period. Twenty patients received mechanical ventilation (10 interventional and 10 control), and 20 did not (10 interventional and 10 control). There were 27 male and 13 female patients; 20 patients were Hispanic, 10 were African-American, and 10 were Caucasian. The mean age was 57.4 years in the interventional group and 52.5 years in the control group. Severity of illness was equivalent in both groups. The mean APACHE II score was 14.3 in the interventional group and 13.8 in the control group. The mean number of cigarette packs smoked per day was 1.2 in the interventional group versus 1.0 in the control group, and the duration of smoking was equivalent in both groups; 24.4 years in interventional group versus 23.3 in the control group. All patients were admitted to the ICU from either a general medical floor or the emergency room. There was no cut-off as to when a patient from a general medical floor could join the study. Interestingly all patients but one were admitted from the emergency room. This patient (from the general medical floor), however, was admitted to the ICU within an hour of being on the general medical floor. It was verified that patients transferred to the ICU from the general medical floors were not already receiving NRT. Patients were admitted with various diagnoses in both groups, and there was no significant difference in the admission diagnoses between the two groups. It was also noted that there was no difference in the reason for intubation between the two groups, with reasons ranging from respiratory failure to airway protection to sepsis. The mean number of days on analgesics was 1.1 in the interventional group versus 2.1 in the control group. The mean number

of days on vasopressors was almost equal at 0.7 in the interventional group and 0.5 days in the control group. The mean number of days on sedation was nearly double in the control group (2.7 days) compared to the interventional group (1.4 days). The mean length of ICU stay decreased by 2.5 days with NRT use. In the interventional group, the mean length of ICU stay was 4.5 days, versus 7 days in the control group. The mean number of days on ventilator also decreased by 1.6 days with NRT use (1.9 days in the interventional group compared to 3.5 days in the control group). None of the patients (in either the interventional or the control group) died while in the study.

Discussion

This study sought to preliminarily address the critical factors in an ICU setting (*i.e.*, need for sedative and analgesics, number of days on the ventilator, and length of ICU stay) by using nicotine replacement patches in the ICU setting with smokers. Nicotine replacement patches have been shown to be the most consistently effective nicotine replacement therapy when it is not coupled with adjuvant behavioral therapy, which is not feasible in the ICU. Importantly, nicotine replacement has been shown to be effective in hospitalized patients in a meta-analysis of 17 double-blind, placebo-controlled studies.⁵ The nicotine patch delivers a constant rate of nicotine transdermally, which will not interfere with other procedures administered in the ICU (*i.e.*, sedation and/or ventilation procedures).

Though not statistically significant, our preliminary results demonstrate a trend toward decreased stay in the ICU when NRT is administered. Although our data indicate neither the number of days on the ventilator nor days using analgesics, vasopressors or sedation were significantly

different between the NRT-treated and placebo groups. More patients are needed to better evaluate whether the patients' agitation levels contributed to the lengths of their ICU stays.

In the general population, NRT has been shown to be highly effective for smoking cessation by limiting the side effects, including agitation, associated with smoking cessation. However, there are limited studies addressing its use in hospitalized patients.^{1,6-8} Mayer and colleagues⁹ reported five cases of agitated delirium in smokers hospitalized for brain injury. The delirium developed 2 to 10 days after smoking cessation and either completely resolved or substantially improved following NRT. In another report, Tran-Van et al¹⁰ describe a patient with restlessness and difficulty being weaned from mechanical ventilation, which was attributed to nicotine withdrawal. The patient's condition improved following NRT.

Although most studies assess NRT as having a positive correlation with death, the literature reveals that the more pertinent outcome to measure is the need for additional sedatives and/or analgesics and then correlating this need to measured agitation levels and the occurrence of adverse events. According to Woods et al,¹¹ in the 2004 study, reducing ICU agitation not only benefits the patient by reducing the need for sedatives and the decreasing the time on the ventilator, but also benefits the cost of treatment for the hospital by minimizing the need for additional medications associated with minimizing patient agitation. Downstream consequences of these sedatives include lowered respiration rate and increased chance of ICU-associated pneumonias.¹¹⁻¹³

138 Additionally, studies have shown that younger patients are more likely to become agitated in the
139 ICU.¹¹ The median age the in the present study was 57.4 (NRT) and 52.3 (no NRT). This age
140 population is not noted for increased risk of agitation when in the ICU and on mechanical
141 ventilation. Therefore, performing a focused study on NRT in a younger ICU population with the
142 focus on preventing agitation and associated adverse events may reveal a greater benefit in the
143 ICU.

144
145 Studies have demonstrated that the patients who sit up, ambulate, and interact with their support
146 network have a lower mortality rate in the ICU.^{12,13} NRT is potentially another means to
147 facilitate this active behavior in the ICU and lessen the need for agitation-induced sedation. Our
148 results indicate a trend in reducing ICU stay and the decreasing the duration of mechanical
149 ventilation.

150
151 Lucidarme and colleagues² described the impact of nicotine abstinence on the clinical course of
152 critically-ill patients receiving mechanical ventilation for at least 48 hours. Their study included
153 144 patients (44 smokers and 100 non-smokers) and showed active smoking to be an
154 independent risk factor for agitation. However, a prospective randomized clinical trial of
155 hospitalized smokers by Lewis and colleagues¹⁴ did not show any difference in mortality
156 between the nicotine patch versus placebo. Because of the paucity of clinical trials demonstrating
157 the benefit of NRT for smoking cessation in ICU patients, NRT is generally used by exclusively
158 by intensivists as a method of easing or preventing withdrawal symptoms.

Cartin-Ceba et al¹⁵ completed a prospective observational study of smokers admitted to the ICU in which they sought to investigate the impact of NRT on critically-ill patients, including hospital mortality (primary outcome), delirium, and cumulative doses of sedation and analgesia (secondary outcomes). A total of 330 active smokers (older than 18 years of age) were evaluated, and 174 received NRT upon admission to the ICU. A total of 14 patients from the group receiving NRT (7.8%) died, as did 10 patients from the non-NRT group (6.3%) – a difference that was not statistically significant ($p = 0.595$). However, the NRT group did experience significantly more delirium than the non-NRT group (average ICU days, 169 [23%] versus 75 [13.1%]; $p \leq .001$). Their results showed that NRT was not associated with increased hospital mortality after adjustment for severity of disease, pack-years of smoking, and do-not-resuscitate status upon ICU admission (odds ratio, 1.6; 95% confidence interval, 0.6 - 4.1; $p = .35$). They noted that a randomized controlled trial was needed to really evaluate these risks and benefits.

A double-blind, placebo-controlled clinical trial by Warner et al¹⁶ reported that routine NRT was not beneficial in the management of perioperative nicotine withdrawal in smokers who underwent elective surgery. Lee and Afessa¹⁷ conducted a retrospective case-control study in which they identified 90 cases (smokers who received nicotine replacement in the first 24 hours of their MICU admission) and 90 controls (smokers who did not receive nicotine replacement), matched for APACHE III score and age. Unadjusted mortality was 20% in those that received nicotine replacement and 7% in those that did not. When adjusted for severity of illness and mechanical ventilation, those who received NRT still had significantly higher mortality (odds ratio 24.6, confidence interval 3.6-167.6). They concluded that NRT was associated with

increased hospital mortality in critically ill patients. Although their findings are striking, this was a single center retrospective study.

Paciullo et al¹⁸ studied the impact of NRT on in-hospital mortality following coronary artery bypass graft surgery. Sixty-seven patients who received NRT were matched with 67 current smokers in terms of baseline demographics and surgical procedures. Mortality was nonsignificantly higher in the NRT group versus the non-NRT smoker group (4.5% vs 0.0%; $p = 0.080$). In a follow-up commentary to Lucidarme et al,² Afessa and Keegan¹⁹ affirm that due to the paucity of data describing nicotine withdrawal in the critically ill, prospective studies are needed to address the issues of mortality, as well as prevention and treatment options.

Although this was a pilot study with a small sample size, the positive-trending results indicate further studies should be performed on a larger scale at this and other institutions to broaden the population of this study. Despite having a broad protocol in which patients from the emergency department or the general medical floor could be included in the study, the majority of patients in this study were admitted to the ICU from the emergency room; the one patient who was not admitted through the emergency room only spent ≤ 1 hour on the general medical floor. In future studies, we aim to evaluate the patient population admitted from the general medical floor to the ICU to compare the results to our present study.

Conclusion

Data supporting the safety or harm of NRT in preventing nicotine withdrawal syndrome in patients admitted to the ICU are very limited. Although the total length of ICU stay and number

of days on ventilator decreased in patients receiving NRT. Statistically the, preliminary data demonstrated no significant beneficial effect. Enrolling more subjects and increasing the study's power could help better define the role of NRT in smokers admitted to the ICU.

Acknowledgements

The authors thank Po-Huang Chyou of the Marshfield Clinic Research Foundation's Biomedical Informatics Research Center for assistance with statistical analysis. They further thank Marie Fleisner of the Office of Scientific Writing and Publication for editorial assistance in the preparation of this manuscript.

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Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	
	Patient admitted to intensive care unit.
	With or without ventilator.
	Informed consent (either by patient or delegate).
	Smoking at least one or more packs of cigarettes per day.
	No contradiction to nicotine use.
Exclusion Criteria	
	Myocardial infarction in last 2 weeks.
	Unstable angina.
	Uncontrolled or serious arrhythmia.
	Severe allergic reaction.

Table 2. Characteristics of patients by the status of nicotine replacement therapy.

Characteristic	Nicotine replacement therapy				P-value *
	Yes		No		
	<i>n</i>	(%)	<i>n</i>	(%)	
Race					NA
Hispanic	10	(50)	10	(50)	
African American	5	(25)	5	(25)	
Caucasian	5	(25)	5	(25)	
Ventilator					1.0000
Yes	10	(50)	10	(50)	
No	10	(50)	10	(50)	

* P-value was derived from the McNemar's test for paired data

Table 3. Results of the nicotine replacement therapy.

	Nicotine replacement therapy												<i>P</i> -value *
	Yes				No				Difference				
	<i>n</i>	Mean	Standard Deviation	Median	<i>n</i>	Mean	Standard Deviation	Median	<i>n</i>	Mean	Standard Deviation	Median	
Age (year)	20	57.4	12.0	58.0	20	52.3	13.3	52.5	20	5.1	14.6	2.0	.1159
APACHE II	20	14.3	9.7	11.5	20	13.8	9.4	12.0	20	0.5	1.1	0.0	.0723
Length of ICU stay (day)	20	4.5	3.8	3.0	20	7.0	5.8	5.5	20	-2.5	6.6	-1.0	.0844
Number of packs per day of cigarettes	20	1.2	0.5	1.0	20	1.0	0.4	1.0	20	0.1	0.7	0.0	.5000
Number of days on ventilator	20	1.9	3.7	0.0	20	3.5	5.3	1.0	20	-1.6	6.3	0.0	.4683
Number of days on analgesia	20	1.1	2.6	0.0	20	2.1	3.8	0.5	20	-1.1	4.5	0.0	.2573
Number of days on vasopressors	20	0.7	1.6	0.0	20	0.5	1.3	0.0	20	0.2	1.9	0.0	.7813
Number of days on sedation	20	1.4	2.5	0.0	20	2.7	4.6	0.5	20	-1.4	5.3	0.0	.4067
Years of smoking	20	24.4	10.2	25.0	20	23.3	10.7	20.0	20	1.1	10.8	0.0	.7906

APACHE = Acute Physiology and Chronic Health Evaluation.

ICU=intensive care unit.

* *P*-value was derived from the Signed Rank test for paired data.