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ORIGINAL ARTICLE

Nicotine replacement therapy in surgical patients

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Abstract

BACKGROUND AND AIMS: The effect in smokers of nicotine withdrawal following surgery may contribute to the development of postoperative delirium. Nicotine is known to increase myocardial oxygen demand, coronary vasoconstriction, and may cause platelet activation leading to thrombosis. All of this can negatively impact postoperative recovery. The aim of this study was to determine whether nicotine replacement therapy can overweigh its negative effects, reduce the incidence of delirium, reduce the need for sedatives/analgesics, and/or shorten the duration of artificial pulmonary ventilation.

METHODS: This prospective randomized single-blind study was performed in a 21-bed ICU. Fifty-two patients (26 intervention/ 26 control) met the inclusion criteria. Patients in the intervention group received a 21mg nicotine patch daily until discharged from the ICU (up to 7 days), patients in the control group received a placebo patch. The incidence of delirium was monitored with the CAM-ICU test. Sedatives/analgesics used in the ICU, and the duration of both artificial ventilation as well as total ICU stay were recorded for both groups.

RESULTS: Nicotine replacement in smokers did not reduce the incidence of delirium in patients who had undergone surgery. Neither did it statistically significantly affect the length of hospitalization, sedation, analgesia, or vasopressors.

CONCLUSION: This study did not confirm the effect of nicotine replacement therapy in reducing the incidence of delirium, it did not shorten the total duration of ICU stay or artificial ventilation and there was no reduced sedation requirement. We therefore saw no beneficial effect in patients receiving nicotine replacement therapy following elective surgery.

Abbreviations:

APV	- Artificial pulmonary ventilation
APPACHE II	- Acute Physiology And Chronic Health Evaluation
CAM-ICU	- The Confusion Assessment Method for the Intensive Care Unit
DSM-5	- The Diagnostic and Statistical Manual
ICDSC	- The Intensive Care Delirium Screening Checklist
n-Ach R	- Nicotinic acetylcholine receptors
NTR	- Nicotine replacement therapy
RACE	- Radical cystectomy

INTRODUCTION

The use of nicotine-containing tobacco products is among the leading causes of preventable death among adults. Available data indicates that it is responsible for approximately 6 million deaths worldwide and a reduction in life expectancy by approximately 10 years (World Health Organization, 2011). Smoking typically starts as a "bad habit" and leads to the development of addiction. Furthermore, there is a growing risk that forced withdrawal of nicotine during hospitalization will lead to symptoms of withdrawal syndrome and the development of delirium.

Postoperative delirium is a manifestation of brain dysfunction and is an acute life-threatening postoperative complication, especially among the elderly. It is one of the most common postoperative complications in the >65 age group. Its incidence varies between 5% and 50% depending on other risk factors of the patient and the degree of surgical stress (American Geriatrics Society, 2015; American Psychiatric Association, 2013).

There are several simple bed-side methods for diagnosing delirium. CAM-ICU (The Confusion Assessment Method for the Intensive Care Unit) have been validated for intensive care and it's validated Czech version (Meagher, 2000; Mitasova, 2010; Confusion Assessment Method for ICU, 2016) was used to monitor delirium in this study. Delirium significantly worsens treatment outcomes in patients, leading to functional status deterioration, long-term cognitive dysfunction, and extends the duration of hospitalization (thereby increasing costs). Although it is an independent predictor of higher patient mortality and morbidity, it is also a condition that can be prevented in up to 40% of patients through appropriate preventive measures (Girard, 2008).

Several risk factors (RF) contribute to the development of delirium, which can be divided into patient-specific and perioperative factors. Patient-specific risks (predisposing RF) are less susceptible to prevention: older than 65 years, hypertension, pre-existing cognitive impairment (especially dementia), functional impairment (auditory or visual), previous history of delirium, and abuse of benzodiazepine, alcohol, or nicotine. Some predisposing RF like a permanent urinary catheter, use of restraints, electrolyte abnormalities and infections – can be mitigated using appropriate preventive measures. Patients with more severe disease (with a higher APACHE score) are more at risk for the development of delirium. The second large group of risk factors are specific perioperative factors based on the degree of surgical stress, length of surgery, blood loss, number of transfusions, or insufficient analgesics (American Psychiatric Association, 2013; Robinson, 2008). These risk factors need to be considered during the preoperative examination to assess the risk of a particular patient developing delirium, so that the necessary preventive measures can be taken.

Withdrawal of nicotine upon admission to the hospital and during subsequent perioperative care may contribute to the development of withdrawal syndrome. Clinical symptoms usually start to appear within 12 hours (sympathicotonia, sweating, headache, restlessness, development of hyperactive delirium), peaking after one week of withdrawal (American Psychiatric Association, 2013; Robinson, 2008).

Smoking has numerous side effects that are caused by a number of toxic or carcinogenic substances and heavy metals contained in cigarette smoke. Nicotine itself is involved in the activation of nicotinic acetylcholine receptors (n-ACh R) in sympathetic nerves, increases the heart rate, blood pressure, cardiac output, and increases the risk of acute coronary events. The question therefore arises whether it is safe to use nicotine replacement to prevent withdrawal syndrome. Transdermal nicotine does not increase cardiovascular risks (Benowitz, 1997). Transdermal nicotine slowly releases lower doses of nicotine than a cigarette. It activates the sympathetic nervous system but given the lower dose, it does not increase the risk compared to smoking, even in clinical studies of patients with acute coronary syndrome. Moreover, unlike smoking, transdermal nicotine does not cause a hypercoagulable state and does not activate platelets. Nonetheless, it does lead to an imbalance between the vasodilating antiplatelet prostacyclin and thromboxane A2 – that have opposing effects (Raja, 2021; Mills, 2014).

The aim of our study was to investigate whether preventive transdermal nicotine substitution can be used to reduce the incidence of symptoms of nicotine withdrawal on elective surgical patients with nicotine dependence following major surgery. The operating hypothesis was that nicotine replacement therapy (NRT) leads to a decreased incidence of delirium. A secondary objective of this study was to determine whether NRT in this cohort is associated with shorter sedation times and shorter duration of artificial pulmonary ventilation (APV) compared to placebo controls.

PATIENTS AND METHODS

This was a randomized, single-blind pilot clinical study. The study took place in 2015–2020 at a 23-bed intensive care unit in the University Hospital Ostrava. Prior to patient randomization, the patient's baseline demographic data (age, gender, BMI) and Fagerström test were monitored (Heatherton, 1991). Following Informed Consent, a total of 52 patients were enrolled on an ongoing basis (26 patients in the intervention group, 26 in the control group). Patients undergoing major surgery who met the inclusion criteria were assigned randomly to one of two groups – the intervention (with a nicotine patch) and the placebo or control groups – within 24 hours of admission to the ICU. The criteria for inclusion or non-inclusion of subjects in the study (Table 1) were assessed during pre-anaesthetic

Tab. 1. Criteria for inclusion / exclusion / early termination of subjects

Inclusion criteria
Patients over 18 years of age.
Assumption of nicotine abstinence, assessed according to the Fagerström nicotine dependence test.
Smoking ≥ 10 cigarettes per day; no more than 30 days have elapsed since the cessation of regular smoking.
Undergoing surgery in the urology, traumatology, orthopaedics or head and neck surgery (including dental surgery) departments, with the assumption of a subsequent stay in the ICU of >24 hours.
Exclusion criteria
Age <18 years.
Patients following neurosurgery, diagnosed craniotrauma, psychiatric illness.
Allergy to nicotine or component of the transdermal nicotine patch or placebo agent.
Patients with a recent myocardial infarction, unstable or worsening angina pectoris or patients with severe cardiac arrhythmias, patients with a recent stroke.
Pregnant and lactating women.
Patients being treated with nicotine-containing products.
Criteria for premature termination
Occurrence of a severe local reaction at the application site of the transdermal patch or dressing with a generalized skin reaction.
The patient's request to terminate participation in the clinical trial.
Occurrence of severe heart rhythm disorders, stroke, angina pectoris, heart attack, pregnancy.
Use of another nicotine-containing product incl. tobacco products.
Death of the patient.

examination of the patient prior to the planned surgery. All patients enrolled in the study were instructed to quit smoking. Patients in the intervention group were given a 21 mg nicotine transdermal patch after randomization (NiQutin CLEAR, OMEGA PHARMA a.s., Brno). The first patch was applied immediately after patient randomization; each additional patch was changed daily in the morning. The transdermal patch was covered with an opaque bandage [Curapor, Lohmann & Rauscher (L&R)] for blinding purposes. This intervention lasted for a maximum of 7 days or as long as the ICU stay, in cases where the ICU stay was shorter. Patients in the control group were given a placebo patch (Hydrocoll, HARTMANN) immediately after randomization. This patch was also applied daily in the morning and the patch site covered with an opaque bandage. This intervention also lasted for 7 days or as long as the ICU stay, in cases where the ICU stay was shorter. The occurrence of delirium was detected using a standard CAM - ICU test and was administered once a day from the day of randomization. No additional pharmacological intervention to prevent delirium was administered to patients in either group.

Data collection

During the clinical trial, the Acute Physiology And Chronic Health Evaluation (APACHE II score), CAM - ICU test, durations of APV and of ICU stay, and patient mortality were monitored in both groups.

Outcomes

The primary endpoint was the incidence of delirium assessed by the CAM-ICU test and the efficacy of NRT to reduce incidence of delirium in smokers in the group of elective surgical patients. Secondary endpoints were duration of sedation, duration of APV and of the ICU stay.

Statistical analysis

The median and range (minimum and maximum) were chosen as the basic descriptors of numerical variables. The analysis of categorical variables was based on the use of absolute and relative frequencies and expressed as percentages. The observed groups were compared using the Mann-Whitney test or Fisher's exact test. All statistical analyses were performed using R software (version 4.0.3, www.r-project.org) and the significance level was set to 0.05. A total of 52 patients were enrolled in the study over nearly six years, 26 in the intervention group and 26 in the placebo group. Both groups were comparable in age with a median age of 58 years in the intervention group and 60 years in the placebo group. Males predominated in both groups (22 and 21 men), with a total of 43 men out of 52 (83%). Patients with different surgical diagnoses before major elective surgeries were randomly assigned to both groups. Severity of illness in both groups were comparable, with a median APACHE II score of 8 in the intervention group, versus 9 in the placebo group. Nicotine dependence as assessed by the

Tab. 2. Characteristics of all evaluation subjects.

MEDIAN (RANGE) or n (%)[a]	All patients (N = 52)
Numeric variable	
Age (y)	59 (22; 77)
BMI	26.6 (16.6; 42.9)
Duration in the study (days)	3 (2; 7)
Duration of hospitalization (days)	3 (2; 46)
Duration of APV (days)	0 (0; 7)
Duration of sedation (days)	0 (0; 7)
Duration of vasopressors (days)	0 (0; 7)
Duration of analgesics (days)	2 (0; 7)
Duration in ICU (days)	3 (2; 46)
APPACHE II	8 (2; 19)
Fagerström test	5 (3; 10)
CAM – ICU – evaluated (days)	3 (2; 7)
CAM – ICU – non-evaluated (days)	0 (0; 2)
Category variable	
Gender (male)	43 (83)
Delirium (yes)	5 (10)
Death (yes)	0 (0)

[a] Median and range (minimum a maximum) or absolute and relative frequency in percentage

Fagerström test was also similar with a median of 5 in the intervention group and 6 in the placebo group. To be included, all patients had to meet the presumption of nicotine dependence (smoking ≥ 10 cigarettes per day), with no more than 30 days since the cessation of regular smoking. (Table 2, 3).

PRIMARY RESULTS

Assuming nicotine abstinence, the main objective of the study was to determine whether nicotine replacement in a group of critically ill patients following major surgery reduces the incidence of delirium. The incidence of delirium in this study was very low, at only 10% [5 patients in total; 2 (8%) in the intervention group and 3 (12%) in the placebo group]. Of the five, 3 were men and 2 were women. In four of these patients delirium occurred following a postoperative complication. One patient developed sepsis following lung decortication, one patient had to be re-operated due to haemothorax after gastrectomy, and anastomosis failed in one patient after radical cystectomy (RACE), and it needed repeated surgery. Only one patient showed signs of withdrawal syndrome (nicotine combined with alcohol) following oesophageal resection. In non-delirious patients the postoperative condition was complicated in only four cases: twice due to a paralytic ileus and twice with a marked elevation of inflammation, that did not however develop into septic shock.

Nicotine substitution in smokers did not reduce the incidence of delirium in our cohort.

SECONDARY RESULTS

The secondary objective of this study was to determine whether NRT would reduce the duration of sedation or the duration of APV, and consequently, the duration of hospitalization. The duration of sedation, analgesia, and vasopressors (norepinephrine) did not differ between the nicotine and placebo groups. Sedation was necessary postoperatively practically only to address restlessness in the delirious 10% of patients, and that too was even between both groups – with nicotine (2 cases, 8%) and without nicotine (3 cases, 12%). Thus, the length of sedation did not differ between the nicotine and placebo groups. However, sedation times were longer in the delirium group (median 7 days) than in patients without delirium (median 0 days). Nonetheless, the overall incidence of delirium in our cohort is so low that it does not allow us to draw statistically significant conclusions. Similarly, we see longer durations of both vasopressor administration (median 5 days vs. 0) and the need for analgesia (median 5 days vs. 2 days) in delirious patients compared to non-delirious patients (Table 4), but there were no differences between the intervention and control groups. There was no difference in the duration of artificial pulmonary ventilation (median 0 days in both groups). The median length of ICU stays (3 days) did not differ between the groups, with the intervention group patients staying for 2–23 days, and patients in the placebo group for 2–46 days. The duration in the ICU was affected by delirium, mainly due to postoperative complications. Patients with delirium remained in the ICU for 7 to 46 days, with a median of 8 days. Patients without delirium stayed for 2–9 days, with a median of 3 days. There was no statistically significant difference even in the overall duration of hospitalization (median for the intervention group of 3 days; median for the placebo group of 4 days; p=0.325).

Nicotine substitution did not statistically significantly affect the duration either of hospitalization, sedation, analgesia, vasopressors, or of APV. The development of delirium following surgical complications (4 out of 5 CAM – ICU positive cases) had a negative impact in terms of extending ICU stay, and the administration of sedation and vasopressors. Only one patient developed withdrawal syndrome.

DISCUSSION

Development of delirium significantly complicates a patient's ailment, increases the need for sedation, and prolongs hospitalization, while increasing mortality and morbidity. However, some of the risk factors can be

Tab. 3. The effect of nicotine therapy on ICU patients

MEDIAN (RANGE) or n (%)[a]	Intervention (N = 26)	Placebo (N = 26)	*p*-value[b]
Numeric variable			
Age (y)	58 (22; 77)	60 (36; 72)	0.640
BMI	26.3 (18.5; 36.6)	27.0 (16.6; 42.9)	0.807
Duration in the study (days)	3 (2; 7)	4 (2; 7)	0.296
Duration of hospitalization (days)	3 (2; 15)	4 (2; 46)	0.325
Duration of APV (days)	0 (0; 7)	0 (0; 7)	0.266
Duration of sedation (days)	0 (0; 7)	0 (0; 7)	>0.999
Duration of vasopressors (days)	0 (0; 5)	0 (0; 7)	0.708
Duration of analgesics (days)	2 (0; 7)	2 (0; 7)	0.738
Duration in ICU (days)	3 (2; 23)	3 (2; 46)	0.369
APPACHE II	8 (2; 15)	9 (2; 19)	0.671
Fagerström test	5 (3; 9)	6 (4; 10)	0.087
CAM – ICU – evaluated (days)	3 (2; 7)	3 (2; 7)	0.363
CAM – ICU – non-evaluated (days)	0 (0; 2)	0 (0; 2)	>0.999
Category variable			
Gender (male)	22 (85)	21(81)	>0.999
Delirium (yes)	2 (8)	3 (12)	>0.999
Death (yes)	0 (0)	0 (0)	---

[a] Median and range (minimum a maximum) or absolute and relative frequency in percentage
[b] *P*-value from the Mann-Whitney or Fisher's exact test

avoided (Awissi, 2013; Paolini, 2011; Matsukami, 2008; Hughes, 2007). Research examining the efficacy of NRT to prevent withdrawal syndrome shows conflicting results, mostly due to retrospective design with selection bias (Wilby, 2014; Sedes, 2011; Cartin-Ceba, 2011), or heterogenous populations (Pathak, 2013; de Jong, 2018).

The aim of this prospective randomized single-blind study was to find out whether nicotine replacement is effective in preventing withdrawal syndrome in elective surgical procedures, and whether it can reduce the incidence of delirium in smokers.

Due to the low incidence of delirium, our study was unable to demonstrate any effect of nicotine substitution in our cohort of 52 patients. The low incidence of delirium (10%; 5 delirious patients out of 52) in this study may be explained by the defining feature of our cohort – patients undergoing elective surgery. Postoperative delirium is reported in 5–50% of cases (American Psychiatric Association, 2013) and reaches up to 80% in critically ill patients with APV (Ely, 2004). The incidence of delirium increases with the severity of the condition and the likelihood of acute disease development. This corresponds to an APACHE II median of 11 in patients with delirium and 8 without delirium. Nonetheless, this is not a statistically significant difference. Our cohort included patients after major surgical procedures requiring hospitalization in the ICU. The surgical procedures included gastrointestinal resections (rectosigma, oesophageal resections, ileocecal resection, oesophageal resection, subtotal gastrectomy, or duodenohemipancreatectomy), thoracic surgery (lobectomy, pneumonectomy), urological procedures (radical cystectomy, kidney or adrenal gland removal, prostate surgery) and orthopaedic procedures (total endoprostheses of large joints). On the other hand, they were all elective procedures undertaken after preoperative preparation of patients. Development of delirium cannot be predicted based on the type of surgery alone – the five delirious patients in our cohort were hospitalized following different surgical procedures (RACE, oesophageal resection and tabularised gastric conduit, lung decortication, subtotal gastrectomy, lobectomy). Comparing the incidence of delirium in surgical patients, 35 out of 224 (15.6%) patients admitted to our clinic over a one-year period (February 2014 – February 2015) developed delirium. This was the lowest incidence compared to medical patients (60% delirium; 15 of 25), or trauma patients (68% delirium; 24 of 35). However, all operated patients were included in the surgical group, i.e., for the most part, patients following acute operations (Kanova, 2017).

Nicotine replacement therapy (NRT) has not been shown to be beneficial in other studies in elective surgical patients. No differences were observed among

Tab. 4. Effect of delirium in ICU patients

MEDIAN (RANGE) or n (%)[a]	Patients with delirium (N = 5)	Patients without delirium (N = 47)	*p*-value
Numeric variable			
Age (y)	54 (46; 62)	60 (22; 77)	---
BMI	25.5 (23.9; 31.6)	26.9 (16.6; 42.9)	---
Duration in the study (days)	7 (7; 7)	3 (2; 7)	---
Duration of hospitalization (days)	8 (7; 46)	3 (2; 9)	---
Duration of APV (days)	1 (0; 7)	0 (0; 6)	---
Duration of sedation (days)	7 (0; 7)	0 (0; 5)	---
Duration of vasopressors (days)	5 (0; 7)	0 (0; 2)	---
Duration of analgesics (days)	5 (0; 7)	2 (0; 7)	---
Duration in ICU (days)	8 (7; 46)	3 (2; 9)	---
APPACHE II	11 (6; 19)	8 (2; 15)	---
Fagerström test	6 (5; 6)	5 (3; 10)	---
CAM – ICU – evaluated (days)	7 (5; 7)	3 (2; 7)	---
CAM – ICU – non-evaluated (days)	0 (0; 2)	0 (0; 2)	---
Category variable			
Gender (male)	3 (60)	40 (85)	---
Death (yes)	0 (0)	0 (0)	---

[a] Median and range (minimum and maximum) or absolute and relative frequency in percentage

116 smokers from a double-blind, placebo-controlled study to reduce perioperative stress due to forced nicotine abstinence (Warner, 2005). The only positive outcome was a reduction in the number of cigarettes smoked in the nicotine group over the 30-day postoperative monitoring period of the study.

It is interesting to compare our cohort with a similarly large cohort (Pathak, 2013) of 40 patients from a 20-bed ICU (slightly more severe; median APACHE II 14.3 vs 13.3%). The objective was to demonstrate that NRT reduces sedative consumption, APV duration, or shortens the overall ICU stay. They report shortened ICU stay (7 days vs 4.5 days) and reduced duration of sedation (2.7 days versus 1.4 days) in the nicotine replacement group. These are not statistically significant results either. From our results, nicotine substitution did not reduce the consumption of sedatives, the duration of APV or the ICU stay in the intervention and control groups. These parameters were affected more by delirium, albeit with a small but comparable incidence in both groups. The development of delirium was not affected by nicotine, but most often by surgical complications (anastomosis dehiscence, sepsis).

Our results were not able to confirm the prediction that nicotine substitution would reduce the incidence of delirium in smokers after surgery. Further, systematic reviews of NRT in hospitalized patients published so far point in the same direction: according to them the preventive use of nicotine substitution cannot be recommended unequivocally. The risk-benefit balance of this intervention should always be assessed individually. Especially in critically ill patients with multiorgan dysfunction, the risks associated with nicotine activation of the sympathetic nervous system (vasoconstriction, arrhythmias, spasms) may outweigh its benefits. In addition, withdrawal symptoms cannot be distinguished from those of benzodiazepine or opioid withdrawal (Wilby, 2014; Kowalski, 2016; Lucidarme, 2010). The results of certain studies paradoxically show a higher incidence of delirious symptoms in the nicotine group (Seder, 2011; Cartin-Ceba, 2011). However, these studies administered nicotine to patients who have a history of higher cigarette consumption, were heavier smokers– broadly, patients with a higher risk of developing delirium. In our study, we eliminated this bias by blinding the nicotine and placebo patch groups. Incidence of delirium was not higher in the nicotine group (8%; 2 cases) compared to the placebo (12%; 3 cases).

LIMITS

Our study is limited mainly by the small group of patients, and due to the low incidence of delirium in elective surgical patients our results are not statistically significant. Our selection resulted in a group of surgical patients before elective procedures, i.e., patients preoperatively optimized. It would be better to design a multicentre study that can enrol a larger number of patients.

CONCLUSION

The results of our study do not confirm the effect of nicotine substitution in elective surgical patients mainly due to the low incidence of delirium in this group of patients. It is always necessary to evaluate the possible benefit of NRT individually, balancing polymorbidity, cardiovascular risks on the one hand with the intensity of addiction on the other. Particular attention should be given to the development of withdrawal syndrome, and measures to deal with it should be initiated in a timely manner. Smoking cessation should be the fundamental consideration. New strategies should be considered in future studies.

AUTHORS CONTRIBUTIONS

TK, NJ, KM: data collection; KM, TK: manuscript writing; KM, TK, NJ: final approval.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest regarding the publication of this ar¬ticle.

The clinical trial was approved by the State Institute for Drug Control [EudraCT number: 2014-003720-43]; Ethical Committee of the University Hospital Ostrava, and registered at ClinicalTrials.gov, ID: NCT03856489. The study was carried out with institutional support for the long-term conceptual development of research organizations (decision no: 1 RVO-FNOs/2014).

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