

# Does nicotine replacement therapy affect the frequency of delirium in patients after isolated myocardial revascularization?

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**Aim** Among cardiac patients, active smokers are not a rarity. Smoking causes a strong addiction and smoking cessation leads to the development of a withdrawal syndrome. Due to forced smoking cessation before surgery, nicotine abstinence may become one of the reasons for the development of delirium in the immediate postoperative period. The study was designed to assess the efficacy of nicotine replacement therapy in the prevention of delirium in smoking patients after isolated myocardial revascularization surgery.

**Methods** From January 2014 to December 2014, 968 patients underwent isolated myocardial revascularization. Four hundred and twenty-eight of the above patients with the length of smoking of more than 10 years were included in the study. Nicotine replacement therapy in the smoking patients consisted of two sequential applications of nicotine patches. The first application was put in the operating room before induction into anesthesia, the second one—after 16 hours in the intensive care unit. The control group of smoking patients, in whom nicotine replacement therapy was not implemented, was formed by the selection method according to the match index with the first group. To form the group, the following criteria were used: sex, age, body mass index, length of smoking, EuroSCORE, left ventricular ejection fraction, concomitant diseases, off-pump coronary artery bypass grafting.

**Results** In the immediate postoperative period the patients of both groups had episodes of delirium and agitation. Delirium developed less frequently in the group of patients receiving nicotine replacement therapy (34.7% vs 55.1%,  $p = 0.05$ ). The average time of mechanical ventilation for patients with nicotine replacement therapy (3 h 35 min) was less than that for patients without nicotine replacement therapy (4 h 10 min). At the same time the groups did not differ from each other by the duration of their stay in intensive care unit, which was only one day.

**Conclusion** Since smoking is a risk factor for the development of delirium, implementation of nicotine replacement therapy in smoking patients who underwent isolated myocardial revascularization can reduce not only the frequency of delirium in the early postoperative period, but also the duration of the ventilator support and the percentage of complications associated with it. myocardium protection; preconditioning; ischemic-reperfusion injury; nitric oxide

**Keywords** nicotine replacement therapy; nicotine withdrawal syndrome; intensive care unit; delirium

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## Introduction

Heavy smokers make up a large share of patients treated at intensive care unit (ICU). Their follow-up is often complicated by a withdrawal syndrome resulting from a sudden refusal from smoking after scheduled cardiac surgery or acute condition leading to a transfer to ICU. A nicotine withdrawal syndrome can manifest itself in the following states: irritation, frustration, depression, unexplained foreboding, insomnia, motor anxiety. These disorders, which last for about 2 to 4 weeks, reach their peaks in the first week after giving up smoking [1]. The nicotine withdrawal syndrome is considered to be a risk factor for development of delirium in patients being treated at ICU [2–4].

Delirium is a clinical syndrome characterized by acute failure of attention, cognitive dysfunction, increased or decreased psychomotor activity and sleep – wakefulness cycle disorder [5].

Delirium is diagnosed in 11 patients (80%) at ICU following cardiac surgery [6–8]. Delirium increases the risk of respiratory failure, sternal instability, nosocomial infections, lethal outcome [6–9]. It also causes functional and cognitive disturbances in immediate and long-term postoperative periods [10]. The nicotine withdrawal syndrome can be effectively managed by nicotine replacement therapy (NRT) [11, 12]. Unfortunately, there are little data on its use in patients undergoing cardiac interventions. Moreover, studies of NRT efficacy in ICU patients have controversial results [13, 14].

Thus, given the relationship between the nicotine withdrawal syndrome and delirium, NRT can be thought of as a method aimed at preventing delirium in cardiac patients. The purpose of our study is to evaluate the efficiency of NRT used to prevent delirium in patients following isolated myocardial revascularization.

## Methods

Our retrospective study included 968 patients who had undergone isolated myocardial revascularization (CABG) at Federal Center for Cardiovascular Surgery (Penza, Russia) from January to December 2014. Non-smokers, patients with incomplete smoking history and smoking history less than 10 years, patients with craniocerebral injury, patients who had suffered from stroke, alcoholics, patients experiencing a 24-hour

complicated postoperative course (resterotomy caused by bleeding, acute coronary syndrome) were excluded from the study. Smokers were selected for NRT with the help of a table made by computer generation of random numbers. NRT consisted of two consecutively prescribed applications of a 25-mg nicotine-containing patch. The first application was performed in the operation suite prior to anesthesia induction, the second one – 16 hours after surgery at intensive care unit.

A coincidence index was used to form the control group with the following criteria to be met: sex, age, body mass index, smoking history, EuroSCORE, left ventricle ejection fraction, concurrent pathologies, off-pump CABG.

CABG was done under combined anesthesia (intravenous and inhalation) according to the protocol. Fentanyl, propofol and rocuronium bromide were first administered and then a patient received volume-controlled ventilation, with  $\text{FIO}_2$  being not less than 60%. Anesthesia was maintained by fentanyl in the total dose not exceeding 20–25  $\mu\text{g}/\text{kg}$  and sevoflurane 1.5–2.5 vol.%. With the pump on, inhalation agent was delivered directly in the oxygenator line 1.5–2.5 vol.%, (MAC 1.3–1.7).

Extracorporeal circulation was put on simultaneously with total heparinization and perfusion ratio 2.8–3.0  $\text{l}/\text{m}^2/\text{min}$  under normothermia (venous blood temperature 36.6–36.7 °C). Mean perfusion pressure was maintained within 60–70 mm Hg. Off-pump CABG was carried out with average arterial blood pressure 70–100 mm Hg. If these indicators deviated, phenylephrine and nitroglycerin were intermittently administered. Following the operation all patients were transferred to ICU for 48 hours, where they were treated in compliance with standard protocols. Monitoring included invasive arterial pressure, central venous pressure, gas and electrolyte composition of arterial and venous blood, as well as complete blood count and biochemical blood assay. Urine flow was measured every hour. Extubation was carried out at RASS 0 consciousness level (Richmond Agitation-Sedation Scale), stable hemodynamics with minimum inotropic/vasopressor support and oxygenation index exceeding 150.  $\text{FiO}_2$  was not more than 50%,

respiratory rate at Continuous Positive Airway Pressure was under 30 per minute, lung capacity was more than 10 ml/kg, negative inspiratory pressure exceeded 20 cm H<sub>2</sub>O. To relieve pain, routine use was made of tramadol in a dose of maximum 300 mg/day in combination with acetaminophen 3 g per day or non-steroidal anti-inflammatory drugs. In the case of acute intensive pain syndrome, the patients received opioid pain relievers (trimeperidine, morphine).

To determine a diagnosis and delirium type, the patients were monitored three times a day. Delirium was diagnosed by an anesthesiologist-intensivist according to ICDSC (Intensive Care Delirium Screening Checklist) criteria [15, 16].

### Statistical analysis

All clinical data were borrowed from the electronic medical history ("Medialog 7.10 B0119"). The results were processed by means of IBM® SPSS® Statistics Version 21 (21.0.0.0) program.

All quantitative distributions were verified by Kolmogorov–Smirnov test, quantile diagrams and

skewness and kurtosis normality tests. The obtained data with asymmetric distributions were compared by means of Wilcoxon non-parametric test for two paired samples.

Qualitative data were analyzed by means of McNemar's test for two paired samples.

A critical significance level was accepted as maximum 0.05. The results of all quantitative variables are presented as a median (Me) and quartiles (P25 and P75), the achieved significance level is shown as (p). The results of all qualitative variables are given as a quantity (n) and a share of the group (%), the achieved significance level as (p). The analysis aimed to determine the presence or absence of a statistically significant dependence of delirium incidence on the application of NRT based on a transdermal patch.

### Results

According to the exclusion criteria, 540 (55.79%) patients out of 968 enrolled were dropped from the study. Forty nine patients out of the remaining 428 received NRT, the NRT<sup>+</sup> group. The control group

**Table 1.** Comparative analysis of patients' intraoperative qualitative and quantitative indicators (n = 98)

Variable	NRT <sup>-</sup> (n = 49)	NRT <sup>+</sup> (n = 49)	p
Sex (male)	49 (100%)	49 (100%)	1
Age (years)	58 (50.5–62.0)	54 (51–61)	0.44
Smoking history (years)	35 (30–40)	35 (30–40)	0.94
Body mass index	29 (26–31.5)	28 (25–32)	0.41
Arterial hypertension	38 (77.6%)	41 (83.7%)	0.61
Hypercholesterolemia	9 (18.4%)	10 (20.4%)	1
Peripheral vascular disease	2 (4.1%)	6 (12.2%)	0.29
Diabetes mellitus	6 (12.2%)	7 (14.3%)	1
Chronic obstructive pulmonary disease	6 (12.2%)	7 (14.3%)	1
Chronic kidney disease	1 (2%)	0 (0%)	1
EuroSCORE (%)	1.97 (1.33–2.73)	1.94 (1.33–2.73)	0.6
Ejection fraction (%)	53 (44–60)	54 (49–60)	0.48
NYHA Heart Failure Classification	2 (2–3)	2 (2–3)	0.13

The patients' groups statistically did not differ in the frequency of repeated admissions to ICU, the number of bed-days in ICU and in-patient stay ( $p > 0.05$ ). Ejection fraction was measured by using the Simpson's method. EuroSCORE, European System for Cardiac Operative Risk Evaluation; NYHA, The New York Heart Association

(NRT) comprised 49 patients matching to those in the first group. The total number of patients to be analyzed amounted to 98 people (see Tables 1 and 2).

The NRT<sup>+</sup> group demonstrated a rarer occurrence of delirium as compared with the control group (34.7% versus 55.1%,  $p = 0.05$ ). The median lung ventilation time in the NRT<sup>+</sup> group (Me = 3 h. 35 min) was lower than that in the control group (Me = 4 h. 10 min),  $p < 0.01$ .

## Discussion

Delirium is not an isolated pathology. It is highly likely a symptom of central nervous system damage, polyetiological in its nature. A common model of delirium development suggests the presence of predisposing and initiating factors, which are triggering ones as well [17]. Such separation enables to use some indicators for preoperative determination of delirium risks, while others can be helpful for modification of peri- and postoperative care. Smoking is a modified factor of delirium risks, while NRT, respectively, is a potentially preventive method. Our study has confirmed this hypothesis. In the group of patients receiving NRT, delirium was observed rarer (34.7% versus 55.1%,  $p = 0.05$ ) and the lung ventilation time, which can be also considered a surrogate marker of delirium, was less in the NRT<sup>+</sup> group (3 h. 35 min against 4 h. 10,  $p < 0.01$ ).

Unfortunately, there are few studies on NRT efficiency in ICU patients, especially those related to delirium prevention, and they are somewhat controversial [13, 14, 18–21]. It should be noted that

in some researches, including those on cardiac patients, NRT was an independent predictor of mortality [13, 14]. D. Seder et al studied 234 ICU patients with subarachnoid hemorrhage. 128 patients received NRT (21 mg nicotine transdermal patches), with 106 patients making up the control group. The groups were heterogeneous, the NRT group consisted of heavy smokers (over 10 cigarettes a day),  $p < 0.001$ ; diabetics,  $p = 0.006$ ; alcoholics,  $p = 0.1$ ; patients suffering from cerebral edema (according to computed tomography),  $p < 0.001$ . Delirium was more frequent in the NRT group (19% versus 7%, odds ratio 3, 30; 95% confidence interval 1.37–7.97,  $p = 0.006$ ). In addition, the NRT group patients more often developed pneumonia (29% versus 17%,  $p = 0.037$ ), pulmonary edema (24% against 9%,  $p = 0.004$ ) and convulsive disorder (9% versus 2%,  $p = 0.024$ ). Mortality at 3 months was much lower in the NRT group (7% versus 17%,  $p = 0.02$ ). Multivariate analysis revealed that NRT reduced the mortality risk (odds ratio 0, 12, 95% confidence interval 0.04–0.37,  $p < 0.001$ ) [18].

R. Cartin-Ceba et al conducted a prospective study on 330 therapeutic patients at ICU. NRT started within 24 hours since admission to ICU. 174 patients received NRT (a 21 mg nicotine-containing transdermal patch), the remainder formed the control. Delirium was more frequently registered in the NRT group (23% versus 13.1%,  $p < 0.001$ ), consequently, this group more often received anxiolytics ( $p = 0.02$ ) and required less physical limitations (38% versus 19.5%,  $p < 0.001$ ). The patients of both groups showed no difference in

**Table 2** Comparative analysis of patients' postoperative qualitative and quantitative indicators (n = 98)

Variable	NRT <sup>-</sup> , n = 49	NRT <sup>+</sup> , n = 49	p
Delirium	27 (55.1%)	17 (34.7%)	0.05
Artificial lung ventilation (hr/min)	4:10 (3:25–5:54)	3:35 (2:30–4:12)	<0.01
Repeated admissions	4 (8.2%)	7 (14.3%)	0.51
Bed days at ICU	1 (1–2)	1 (1–1)	0.29
Total bed days of inpatient stay	10 (8.5–13)	11 (8–13)	0.63

ICU, intensive care unit

the indicators of mortality, duration of ICU stay, lung ventilation time [19]. Similar results were achieved by M.A. Gillies et al, their ICU general patients subjected to NRT more often experienced episodes of delirium and agitation (25.7% versus 7.1%,  $p < 0.001$ ) [20]. A. Kerr et al noted in their study that the NRT group patients more frequently received antipsychotics (34.1% versus 11.1%,  $p < 0.01$ ), needed more physical limitations or fixation (29.4% versus 9.5%,  $p < 0.01$ ), elongated lung ventilation time (2.56 days versus 1.44 days,  $p = 0.012$ ) [21]. A slight number of studies (of a case-control and one randomized studies) confirm NRT efficacy in delirium prevention. S.A. Mayer et al described 5 episodes of delirium completely aborted within 24 hours after NRT application [22]. D. Tran-Van et al reported that a patient with nicotine withdrawal syndrome, psychomotor agitation and prolonged lung ventilation time demonstrated positive dynamics after NRT [23]. A randomized placebo-controlled study by V. Pathak et al included 40 ICU general patients, with 20 of them receiving NRT for 48 hours at ICU (a 21 mg nicotine patch). As surrogate markers, the authors used the number of days the patients had spent on the lung machine and the number of days when they needed analgesics and anxiolytics. The NRT group patients showed a reduction in the ventilation time (1.9 versus 3.5 days,  $p = 0.47$ ) and a need in analgesics (1.1 versus 2.7 days,  $p = 0.26$ ) and anxiolytics (1.4 versus 2.7 days,  $p = 0.41$ ). All the results turned out to be statistically insignificant, which, according to the authors, could be explained by a small sample of patients [24]. The authors of systematic reviews on NRT application do not recommend its routine usage in ICU. In their opinion, nicotine replacement therapy is indicated for a limited cohort of patients, where potential benefits are greater than the risk of its application. To make final conclusions on NRT efficacy, there is a need in well-organized randomized studies involving as many participants as possible [25, 26].

## Conclusion

Since smoking is a modified factor for delirium development, nicotine replacement therapy for smoking patients undergoing isolated myocardial revascularization might reduce not only the incidence

of delirium in early follow-up but the duration of artificial lung ventilation and the percentage of related complications as well.

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## Conflict of interest

Authors declare no conflict of interest.

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