

# Transcutaneous nicotine does not prevent postoperative nausea and vomiting: a randomized controlled trial

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- There is empirical evidence that smokers are less likely to suffer from postoperative nausea and vomiting (PONV).
- Tobacco smoke is known to induce enzymes, for instance, cytochrome P450, and this may partially explain the PONV-protecting effect of smoking.
- Chronic exposure to nicotine that is contained in the tobacco may lead to a desensitization of central nicotine receptors, and, subsequently, to an increased tolerance to the emetogenic effects of surgery and anaesthesia.

## WHAT THIS STUDY ADDS

- In non-smokers undergoing surgery under general anaesthesia, pre-operatively administered transcutaneous nicotine did not decrease the incidence of PONV within 24 h.
- Patients receiving nicotine had a tendency to develop PONV symptoms earlier than controls.
- Exposure to transcutaneous nicotine significantly increased the risk of insomnia during the first postoperative night.

## AIMS

There is empirical evidence that smokers are less likely to suffer from postoperative nausea and vomiting (PONV). We sought to investigate whether transcutaneous nicotine prevents PONV.

## METHODS

Non-smokers receiving general anaesthesia for surgery were randomly allocated to Nicotinell® Patch 10 cm<sup>2</sup> (TTS 10), containing 17.5 mg of nicotine (average delivery rate, 7 mg 24 h<sup>-1</sup>) or matching placebo patch. Patches were applied 1 h before surgery and were left *in situ* until 24 h after surgery (or until the first PONV symptoms occurred).

## RESULTS

We randomized 90 patients (45 nicotine, 45 placebo). In the post-anaesthetic care unit, the incidence of nausea was 22.2% with nicotine and 24.4% with placebo ( $P = 0.80$ ), and the incidence of vomiting was 20.0% with nicotine and 17.8% with placebo ( $P = 0.78$ ). Cumulative 24 h incidence of nausea was 42.2% with nicotine and 40.0% with placebo ( $P = 0.83$ ), and of vomiting was 31.1% with nicotine and 28.9% with placebo ( $P = 0.81$ ). PONV episodes tended to occur earlier in the nicotine group. Postoperative headache occurred in 17.8% of patients treated with nicotine and in 15.6% with placebo ( $P = 0.49$ ). More patients receiving nicotine reported a low quality of sleep during the first postoperative night (26.7% vs. 6.8% with placebo;  $P = 0.01$ ).

## CONCLUSIONS

Non-smokers receiving a prophylactic nicotine patch had a similar incidence of PONV during the first 24 h and tended to develop PONV symptoms earlier compared with controls. They had a significantly increased risk of insomnia during the first postoperative night.

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## Keywords

anaesthesia, nicotine, postoperative nausea and vomiting, prevention

## Received

6 August 2010

## Accepted

24 October 2010

## Introduction

Postoperative nausea and vomiting (PONV) is a disorder that has been frequently underestimated because of its self-limiting character, and since it never becomes chronic and almost never kills. However, serious complications related to vomiting have been described [1]. In 1998, 10% of the French population underwent general anaesthesia [2]. Since there is evidence that 20% to 30% of surgical patients are suffering from PONV symptoms despite the use of modern anaesthetics [3], it may be inferred that PONV remains a major healthcare burden.

Today, several groups of drugs are recognized as truly useful, alone or in combination, for the control of PONV. Among those are corticosteroids, serotonin (5-HT<sub>3</sub>) receptor antagonists, and dopamine (D<sub>2</sub>) receptor antagonists [4]. However, none of these is universally effective; each has advantages and disadvantages, and none can be regarded as a gold-standard. Thus, there is a need for alternative molecules that may further improve the control of PONV.

One strategy to decrease the incidence of PONV is to identify patients at high-risk of developing PONV symptoms and subsequently to target pharmacologic prophylaxis [5]. Identification of predictive factors for PONV has been the subject of many studies [6–8]. They mainly confirmed what clinicians have felt for a long time, namely that female gender, opioid use or a positive history of PONV or motion sickness increased the likelihood of PONV. However, new knowledge was that smokers were less likely to suffer from PONV than non-smokers. At first view this was an unexpected finding since it was well known that adverse effects related to first exposure to low nicotine concentrations or on exposure to very high nicotine concentrations included nausea and vomiting. However, tobacco smoke is known to induce enzymes, for instance, cytochrome P450 [9], and this may partially explain the PONV-protecting effect of smoking. An alternative explanation would be that chronic exposure to nicotine that is contained in the tobacco would lead to a desensitization of central nicotine receptors, and, subsequently, to an increased tolerance to the emetogenic effects of surgery and anaesthesia. This begs the question as to whether in nicotine-naïve patients a short pre-operative exposure to nicotine may decrease the likelihood of PONV. We set out to test this hypothesis in a clinical trial.

## Methods

### *Patient selection, study drug administration and anaesthetic management*

This randomized, placebo-controlled trial was approved by the institutional Ethics Committee and the Swiss agency for therapeutic products (Swissmedic), and was registered at clinicaltrials.gov (identifier: NCT00553709). Written informed consent was obtained from all patients.

We recruited non-smokers (or ex-smokers who had not been smoking for more than 2 years), ASA physical status I or II, aged 18 to 80 years, scheduled for elective inpatient surgery (ear, nose and throat, lumbar disc, abdominal) under general anaesthesia. Patients receiving nicotine replacement therapy, needing prolonged postoperative intubation or nasogastric tube, having hypersensitivity of the skin to nicotine or one of the components of the patch, with systemic cutaneous disease, unstable angina pectoris, recent myocardial infarction, severe arrhythmia, recent cerebral vascular accident, parkinsonism, renal or hepatic failure, diabetes, uncontrolled arterial hypertension, hyperthyroidism, or gastroduodenal ulcer, and pregnant and breastfeeding women were not included in the study.

Patients and investigators were blinded to the study drug. Study medications were randomized in blocks of ten (five nicotine and five placebo) using a computer program by the pharmacy of Geneva University Hospitals and were kept concealed in a neutral opaque cover. Patients were allocated to one of two groups. In the nicotine group, patients received a Nicotinell® Patch 10 cm<sup>2</sup>, containing 17.5 mg of nicotine, with an average delivery rate of 7 mg nicotine 24 h<sup>-1</sup> (= TTS 10). This is the smallest dose of transdermal nicotine patch available on the Swiss market. We expected the nicotine load of this patch size to be of low and acceptable toxicity in non-smoking adults. Controls received a matching placebo patch. Patches were applied on to the thorax or the upper arm and secured with adhesive tape (Mefix®, Mölnlycke Health Care US, Norcross) at the time of premedication with oral midazolam 7.5 mg 1 h prior to induction of anaesthesia. Patches were left *in situ* until 24 h after surgery, or until the first PONV episode occurred.

General anaesthesia was induced with thiopental 3 to 5 mg kg<sup>-1</sup> or propofol 1.5 to 2.5 mg kg<sup>-1</sup>. Tracheal intubation was facilitated with rocuronium 0.6 mg kg<sup>-1</sup> or atracurium 0.5 mg kg<sup>-1</sup>. Anaesthesia was maintained with isoflurane (0.5 to 2.5%) or sevoflurane (2 to 4%). Propofol for maintenance was not permitted. The choice of nitrous oxide was left to the discretion of the anaesthetist who was in charge of the patient. Intra-operative analgesia was with sufentanil 0.2 to 0.4 µg kg<sup>-1</sup> or fentanyl 1 to 2 µg kg<sup>-1</sup>. Neuromuscular blockade was reversed with neostigmine 50 µg kg<sup>-1</sup> and glycopyrrolate 10 µg kg<sup>-1</sup> if deemed necessary by the anaesthetist who was in charge of the patient. Prophylactic anti-emetics (D<sub>2</sub>-receptor antagonists, steroids, 5-HT<sub>3</sub> receptor antagonists) were not allowed before, during or after surgery. After surgery, patients stayed in the postoperative anaesthesia care unit (PACU) for about 2 h and were then transferred to the ward. Postoperative analgesia was with morphine, paracetamol, and ketorolac or ibuprofen.

### *Measurements*

The primary endpoint of the study was the cumulative incidence of PONV (i.e. any nausea and/or vomiting

symptom) within 24 h. Nausea was defined as an unpleasant feeling of sickness in the stomach, often associated with an urge to vomit. Any symptom and sign of nausea (independent of intensity) was considered as nausea. Vomiting was defined as the act of regurgitation of stomach contents. Retching was regarded as vomiting. Nausea, retching and vomiting were evaluated through direct questioning of the patient by a research nurse blinded to treatment allocation. At 24 h, ward charts were reviewed for additional information on nausea, vomiting and anti-emetic rescue treatment. Patients who were vomiting or nauseous were considered as prevention failures and were analysed as such. Patients with PONV symptoms received anti-emetic rescue treatment (intravenous ondansetron 4 mg or intravenous droperidol 0.5 to 1 mg), and their patch was removed immediately.

Secondary endpoints were any adverse effects that were possibly related to the nicotine exposure, such as headache or cardiovascular adverse effects (arterial hypertension, defined as a  $\geq 20\%$  increase in systolic blood pressure compared with pre-operative values, tachycardia, defined as a  $\geq 20\%$  increase in heart rate compared with pre-operative values, arrhythmia, angina). Quality of sleep was measured after the first postoperative night using a 0 to 10 cm visual analogue scale (0 = not sleeping at all, 10 = excellent sleep). Scores below 4 were regarded as inappropriate sleep quality and the scale was subsequently dichotomized into insomnia ( $\leq 4$ ) and appropriate quality of sleep ( $>4$ ).

### Analyses

All patients randomized to receive nicotine patch or placebo were included in the intention-to-treat analysis. Baseline demographic characteristics and outcomes were described as frequencies, proportions or means with standard deviation (SD). Baseline categorical and numerical variables were compared with Chi-square, Fisher's exact test and the unpaired Student's *t*-test. Analysis of the primary endpoints (incidence of PONV, nausea or vomiting within 24 h) and secondary endpoints (headache, cardiovascular adverse effects, insomnia) was done with Chi-square and Fisher's exact test for expected values  $<5$ . Results were expressed as proportions, odds ratios (OR) with 95% confidence intervals (CI) and *P* values. Time to first symptoms of nausea and vomiting were described graphically using Kaplan-Meier survival curves, summarized by median times to event with inter-quartile ranges, and compared by the log-rank (Kaplan-Meier) and Mann-Whitney (medians) test. A two-tailed *P* value  $< 0.05$  was considered statistically significant.

Sample size was calculated on a cumulative expected incidence of PONV within 24 h in controls of 30%. A decrease of that incidence to 10% with transdermal nicotine (i.e. an absolute risk reduction of 20%) was regarded as a clinically relevant improvement in this context [3]. For a 80% power and a 0.05 significance level (Chi-Square test),

90 patients were needed in both active and control groups to test this hypothesis. We intended to include 100 patients in each group to allow for dropouts and study withdrawals. Analyses were performed with Software PASS (PASS/NCSS 2000, NCSS Corp., Kaysville, UT).

### Results

During a 24 month period, 260 eligible patients were invited to take part in this trial but only 90 (34.6%) eventually agreed. The recruitment rate was unexpectedly low. Some patients refused to participate spontaneously since they feared adverse effects due to the nicotine and others worried about becoming addicted to nicotine. The low recruitment rate and expiring patches motivated us to terminate the study prematurely after having included 90 patients. When recruitment was stopped, the cumulative 24 h PONV incidence in controls was 53%, and thus almost twice as high as expected. A *post hoc* power analysis revealed that the final study cohort of 90 randomized patients still had an 80% power at a 0.05 significance level to detect a 30% difference between the two groups in the 24 h incidence of PONV.

The 90 included patients were randomized into two equal groups of 45 each; all received the assigned study treatment (Figure 1). There were two dropouts in the placebo group; one patient refused the patch application and one received intrathecal anaesthesia.

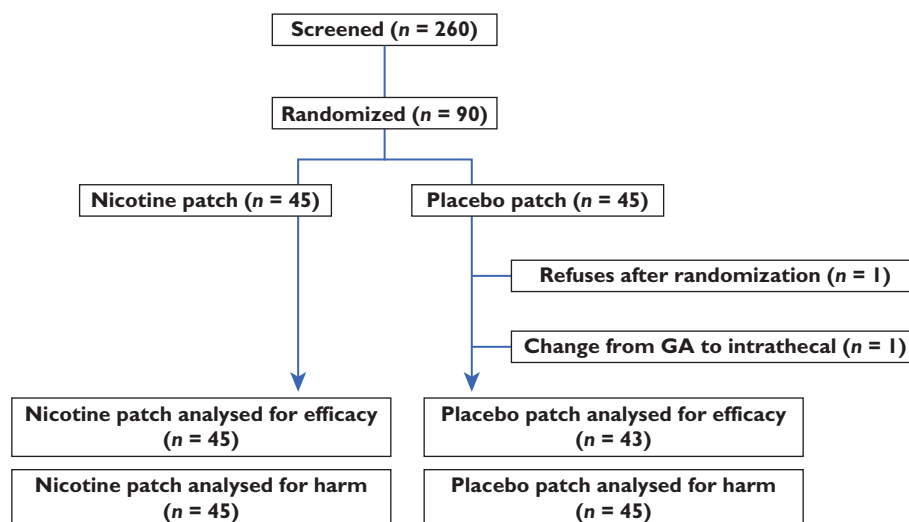
There were no differences between the groups with respect to gender, age, weight, ex-smoker status, PONV risk factors, type of surgery, induction agent or the use of nitrous oxide or neostigmine (Table 1). All patients received opioids postoperatively.

Neither in the PACU nor within 24 h was there any significant difference in nausea or vomiting rates between patients treated with nicotine or controls (Table 2, Figure 2). Cumulative 24 h incidence of PONV was 68.9% with nicotine and was 53.3% with placebo (OR 1.93, 95% CI 0.81, 4.58, *P* = 0.13). The 24 h vomiting incidence was 31.1% with nicotine and 28.9% with placebo (OR 1.11, 95% CI 0.45, 2.74, *P* = 0.81). The 24 h incidence of nausea was 42.2% with nicotine and 40.0% with placebo (OR 1.09, 95% CI 0.47, 2.53, *P* = 0.83) (Table 2).

Nicotine treated patients tended to have their first episodes of nausea and vomiting earlier than controls, but differences did not reach statistical significance (Table 3). No patient had a first episode of nausea or vomiting after 24 h.

In the placebo group, seven of 45 (15.6%) patients were ex-smokers and of those, four (57.1%) developed PONV symptoms. In the nicotine group, eight of 45 (17.8%) patients were ex-smokers and of those, seven (87.5%) developed PONV symptoms (*P* = 0.28).

There was no difference between groups in the incidence of cardiovascular adverse effects or postoperative



**Figure 1**

Flow chart. GA, general anaesthesia

**Table 1**

Baseline comparative patient characteristics and procedures

	Placebo n = 45	Nicotine n = 45	Odds ratio (95% CI) for group difference	P value
<b>Patients</b>				
Age (years)*	46.8 (15.1)	41.8 (13.6)	–	0.12
Weight (kg)*	73.3 (15.0)	74.1 (15.2)	–	0.80
Female gender	17 (37.8%)	20 (44.4%)	1.31 (0.56, 3.05)	0.52
Non-smoker	38 (84.4%)	37 (82.2%)	0.85 (0.28, 2.58)	0.77
Ex-smoker	7 (15.6%)	8 (17.8%)	1.17 (0.38, 3.56)	0.70
<b>PONV risk factors</b>				
PONV history	15 (33.3%)	12 (26.7%)	0.72 (0.29, 1.79)	0.49
Motion sickness	13 (28.9%)	14 (31.1%)	1.11 (0.45, 2.74)	0.81
Migraine	14 (31.1%)	17 (37.8%)	1.34 (0.56, 3.21)	0.50
<b>Surgery</b>				
Ear, nose and throat	23 (51.1%)	26 (57.8%)	1.30 (0.57, 3.01)	0.52
Lumbar disc	4 (8.9%)	1 (2.2%)	0.23 (0.02, 2.17)	0.16
Abdominal	16 (35.6%)	18 (40.0%)	1.20 (0.51, 2.83)	0.66
<b>Anaesthesia</b>				
Thiopentone	1 (2.2%)	1 (2.2%)	1.00 (0.06, 16.49)	1.00
Propofol	42 (93.3%)	44 (97.8%)	3.14 (0.31, 31.42)	0.30
Nitrous oxide	18 (40.0%)	18 (40.0%)	1.00 (0.43, 2.32)	1.00
Neostigmine	9 (20.0%)	15 (33.3%)	2.00 (0.76, 5.21)	0.15

\*Data are means (SD). PONV, postoperative nausea and vomiting.

headache (Table 4). More patients receiving nicotine reported a low quality of sleep (visual analogue scale  $\leq 4/10$ ) during the first postoperative night (26.7% with nicotine vs. 6.8% with placebo,  $P = 0.01$ ).

## Discussion

In non-smokers undergoing surgery under general anaesthesia, a low dose of pre-operatively administered transcutaneous nicotine did not decrease the incidence of PONV

within 24 h. Patients receiving nicotine had a tendency to develop PONV symptoms even earlier and they had a lower quality of sleep during the first postoperative night. No other drug-related adverse effects were observed.

Basic mechanisms underlying nicotine action may help to understand the relationship between nicotine and emesis. Nicotine is a small alkaloid that can mimic the effects of the endogenous neurotransmitter acetylcholine. When nicotine binds on acetylcholine receptors in the central nervous system it perturbs the functioning of the neuronal network. Nicotine exerts both adverse and ben-

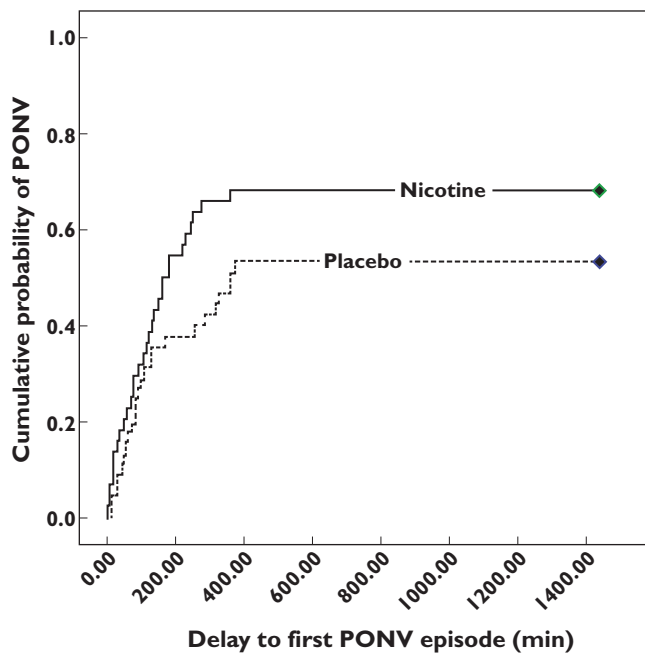


**Table 2**

Postoperative nausea and vomiting (PONV) outcomes

	Placebo <i>n</i> = 45	Nicotine <i>n</i> = 45	Odds ratio (95% CI) for group difference	<i>P</i> value
Nausea in PACU	10 (22.0%)	11 (24.4%)	1.13 (0.42, 3.01)	0.80
Vomiting in PACU	8 (17.8%)	9 (20.0%)	1.15 (0.40, 3.32)	0.78
Nausea within first 24 h	18 (40.0%)	19 (42.2%)	1.09 (0.47, 2.53)	0.83
Vomiting within first 24 h	13 (28.9%)	14 (31.1%)	1.11 (0.45, 2.74)	0.81
PONV within first 24 h	24 (53.3%)	31 (68.9%)	1.93 (0.81, 4.58)	0.13
Anti-emetic rescue medication	23 (51.5%)	26 (57.8%)	1.30 (0.57, 3.00)	0.52

PACU, post-anaesthesia care unit; PONV, postoperative nausea and/or vomiting (including retching)

**Figure 2**

Cumulative probability of postoperative nausea and vomiting (PONV) with nicotine and placebo. Difference between groups:  $P = 0.17$  following log-rank test

eficial effects. Adverse effects include nausea and vomiting and are observed on first exposure to low nicotine concentrations or on exposure to very high nicotine concentrations. The acute emetic effects of nicotine have been well documented. Extreme cases are represented by tobacco field workers who develop the so-called 'green tobacco sickness' [10]. Increased tolerance to the adverse effects of nicotine can, however, be observed during prolonged exposure to this alkaloid. This may explain why smokers experience no repulsion when exposed to tobacco fumes.

The effect of tobacco, and more specifically nicotine, on outcome after surgery has been studied before. Studies investigating risk factors for PONV have consistently reported that non-smokers were at higher risk of develop-

ing nausea and vomiting after surgery compared with smokers [6–8]. A recently published observational study reported on a 50% reduction in the risk of PONV in patients who were chronically smoking and in patients who were snuffing tobacco. This reduction in risk was independent of gender [11]. These observations indicate that substances in the tobacco that are administered by both the inhalational (smoking) and the non-inhalational (snuffing) route might be responsible for the anti-emetic effect of tobacco after surgery. This decreases the likelihood of carbon monoxide or other inhaled substances as being responsible for the reduction of PONV in smokers.

A possible explanation for the lower incidence of PONV in smokers may be that smokers are more resistant to emetogenic stimulations in general, and therefore may support the emetogenic effect of nicotine better than non-smokers. Consequently, they may be more prone to develop an addiction to tobacco and, subsequently, to become chronic smokers. Nicotine absorption might therefore not act as an anti-emetic but rather represent a marker for natural resistance to emetogenic substances and to PONV in general. One may therefore hypothesize that the non-smokers included in the present study were all at a similar risk for developing PONV and those who were exposed to a low dose of the emetogenic nicotine expressed a tendency towards more PONV symptoms, or at least towards earlier PONV. However, the analysis of the subpopulation of ex-smokers in our study did not support this hypothesis.

Others have reported on the effect of nicotine administration on PONV before. In an observational study Ionescu *et al.* compared non-smokers, ex-smokers who received a nicotine patch containing 16.6 mg nicotine 1 h before surgery and active smokers undergoing laparoscopic cholecystectomy [12]. The incidence of PONV was lower in the group of ex-smokers who had received the nicotine patch (20%) and the active smokers (32%) compared with the non-smokers who had not received nicotine (76%). These data suggested that both chronic tobacco consumption and nicotine administration in non-smokers reduced the incidence of PONV. However, these results need to be interpreted carefully, since due to the

**Table 3**

Time to first episodes of nausea and vomiting

	Placebo n = 45	Nicotine n = 45	P value*
Time to first nausea episode (min)	120.0 (53.5–293.0)	119.0 (55.0–160.0)	0.65
Time to first vomiting episode (min)	99.0 (52.5–324.5)	62.5 (12.0–209.2)	0.19

Data are medians (inter-quartile range). \*P value following Mann-Whitney.

**Table 4**

Adverse effects

	Placebo n = 45	Nicotine n = 45	Odds ratio (95% CI) for group difference	P value
Headache	8 (17.8%)	7 (15.6%)	0.72 (0.29, 1.79)	0.49
Insomnia*	3 (6.8%)	12 (26.7%)	5.09 (1.32, 19.5)	0.01
Cardiovascular†	5 (11.1%)	1 (2.2%)	0.18 (0.02, 1.62)	0.09
Any‡	16 (35.6%)	14 (31.1%)	0.81 (0.34, 1.96)	0.65

\*Visual analogue scale <4/10. †Arterial hypertension, tachycardia, arrhythmia, angina. ‡Composite endpoint.

observational design of that study, selection and observer bias cannot be ruled out.

Two previously published randomized trials studied the potential analgesic efficacy of transdermal nicotine in non-smokers undergoing surgery [13, 14]. Both studies reported on PONV symptoms as secondary outcomes. Habib *et al.* randomized 90 non-smokers undergoing radical prostatectomy under general anaesthesia to receive a similar patch of nicotine as in our study (releasing 7 mg of nicotine per 24 h) or placebo. In the nicotine group, cumulative morphine consumption at 24 h was significantly reduced but there was no difference in pain intensity. There was no difference between groups in the incidence of PONV or the need for rescue anti-emetics despite the decreased morphine consumption in the nicotine group. Maximum nausea verbal rating scale scores were even higher in the nicotine group. There were no significant differences between the groups in postoperative heart rate, arterial blood pressure, respiratory rate or oxygen saturation, and there were also no significant differences between the two groups in the quality of sleep [13].

Hong *et al.* randomized 40 patients undergoing general surgery to a transdermal patch that delivered 5, 10 or 15 mg nicotine per 16 h or placebo [14]. Patches were applied immediately before surgery. Patients treated with nicotine reported lower pain scores when compared with those treated with placebo for 5 days after surgery. There was no increased benefit of nicotine with doses larger than 5 mg. There was a trend suggesting an increase in the incidence of nausea with nicotine. Finally, there were no differences in heart rate or arterial blood pressure between the

two groups during the first hour after surgery, or in the degree of sedation [14].

Our study has limitations. Firstly, we did not measure plasma concentrations of nicotine or its main metabolite, cotinine. These could be regarded as convincing evidence of successful absorption, and thus as a basis for a biological effect, in patients who received transdermal nicotine. There are, however, several arguments in favour of an appropriate nicotine absorption in our study despite lacking plasma concentrations. For instance, we used a patch that has been commercially available for the prevention of withdrawal symptoms for many years. The pharmacokinetics of transdermal nicotine have been studied extensively [15]. Also, Habib *et al.* who studied the effect of transdermal nicotine on postoperative pain, were using a similar nicotine patch to ours and they were able to quantify nicotine concentrations in the plasma [13]. Finally, in our double-blind study, nicotine-treated patients reported on impaired quality of sleep during the first postoperative night. Insomnia is a well-known adverse effect of transcutaneous nicotine application in nicotine-naïve volunteers [16]. In non-smoking volunteers performing boring tasks under experimental conditions, transdermal nicotine was shown to act as a stimulant and to prevent an increase in fatigue [17]. Thus, this centrally mediated adverse effect that was observed in our study suggests strongly that the nicotine must have been well absorbed in those patients who had received nicotine transdermally. Premature termination must be regarded as a further limitation of our study. Recruitment appeared to be much more difficult than expected and this may have reflected the reluctance of nicotine-naïve patients to accept nicotine as a treatment

for PONV. Stopping a trial early has the potential to exaggerate the magnitude of benefit [18]. We do not know how this translates into an equivalence study. We were unable to show any benefit with nicotine despite a much higher baseline risk than expected. We may assume that, in view of the high baseline risk, it is unlikely that the results of our study would have been in favour of the nicotine treatment had we randomized more patients. Finally, a potential limitation of our study related to the choice of timing and dosing of the nicotine administration. Our rationale was to choose the minimal effective dose that would not provoke unacceptable adverse effects in nicotine-naïve patients but would have a beneficial effect on PONV. Consequently we chose the lowest dose patch that was commercially available. We applied the patches shortly before start of surgery; based on the well-studied pharmacokinetics of transdermal nicotine administration [15], we expected plasma concentrations to build up during the surgical procedure while the patients were still under general anaesthesia and to be maintained at steady state for several hours postoperatively. However, it cannot be excluded that the chosen dose was too low. None of the patients reported on nicotine-related adverse effects before induction of anaesthesia. This suggests that nicotine-naïve patients may be exposed to higher doses of transdermal nicotine. We do not know whether a higher dose of nicotine or an earlier time point of patch administration before surgery (with subsequently a longer exposure to nicotine), would have changed our results.

Our findings have implications for future research. In non-smokers, a single short administration of a small dose of transdermal nicotine does not seem to have a PONV-preventing effect. Also, previous studies have suggested that not only smokers but also individuals who are snuffing tobacco are protected against PONV [11]. These findings suggest that it may not be the smoking status *per se* that should be regarded as a predictive factor for PONV [7]. It may also be inferred that within tobacco, it is not the nicotine that has a relevant protective effect against emesis after surgery. There is some evidence that regular alcohol consumers are less likely to develop PONV symptoms after surgery [19]. This may simply indicate that regular exposure to multiple exogenous toxins, such as alcohol or tobacco, protects to some extent from the detrimental metabolic and pharmacologic impact of surgery and anaesthesia. Further research should elucidate what substances within the tobacco have a protective effect against PONV. It cannot be excluded either that in our study, exposure time was too short. It may be that in order to desensitize nicotine receptors to a relevant degree in nicotine-naïve subjects, the nicotine patch would have to be applied days and perhaps even weeks before surgery. This, however, is not feasible in daily clinical practice. Also, there is a risk, albeit small, that longer-term administration of nicotine in nicotine-naïve subjects may induce nicotine dependence.

In summary, in non-smokers undergoing surgery under general anaesthesia, a low dose of transcutaneous nicotine, administered shortly before surgery, did not decrease the incidence of nausea and vomiting within the first 24 h postoperatively. Patients receiving transcutaneous nicotine tended to have nausea and vomiting symptoms even earlier and they suffered more often from insomnia during the first postoperative night. Transcutaneous nicotine cannot be recommended as an anti-emetic prophylaxis in surgical patients.

## Competing interests

There are no competing interests to declare.

*We are grateful to Ms Béatrice Gil-Wey, Division of Anaesthesiology, University Hospitals of Geneva, for her role as a research assistant. The study was funded by institutional funds. The nicotine and placebo patches were kindly provided by LTS Lohmann Therapie-Systeme AG, Andernach, Germany.*

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