Effects of a Perioperative Smoking Cessation Intervention on Postoperative Complications

A Randomized Trial

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Objective: To determine whether an intervention with smoking cessation starting 4 weeks before general and orthopedic surgery would reduce the frequency of postoperative complications.

Summary Background Data: Complications are a major concern after elective surgery and smokers have an increased risk. There is insufficient evidence concerning how the duration of preoperative smoking intervention affects postoperative complications.

Methods: A randomized controlled trial, conducted between February 2004 and December 2006 at 4 university-affiliated hospitals in the Stockholm region, Sweden. The outcome assessment was blinded. The follow-up period for the primary outcome was 30 days. Eligibility criteria were active daily smokers, aged 18 to 79 years. Of the 238 patients assessed, 76 refused participating, and 117 men and women undergoing surgery for primary hernia repair, laparoscopic cholecystectomy, or a hip or knee prosthesis were enrolled.

Intervention: Smoking cessation therapy with individual counseling and nicotine substitution started 4 weeks before surgery and continued 4 weeks postoperatively. The control group received standard care. The main outcome measure was frequency of any postoperative complication.

Results: An intention-to-treat analysis showed that the overall complication rate in the control group was 41%, and in the intervention group, it was 21% ($P = 0.03$). Relative risk reduction for the primary outcome of any postoperative complication was 49% and number needed to treat was 5 (95% CI, 3–40). An analysis per protocol showed that abstainers had fewer complications (15%) than those who continued to smoke or only reduced smoking (35%), although this difference was not statistically significant.

Conclusion: Perioperative smoking cessation seems to be an effective tool to reduce postoperative complications even if it is introduced as late as 4 weeks before surgery.

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Postoperative complications are a major concern after scheduled surgery, and smoking is known to increase the frequency of complications. Negative effects on complication rates among smokers have been found in hernia surgery,[1–3] gastrointestinal surgery,[4–7] orthopaedic surgery,[8–10] plastic reconstructive surgery,[11–13] gynecologic surgery,[14] vascular surgery,[15] and minor surgical procedures.[16,17] In an experimental study on healthy subjects, smoking cessation 4 weeks before skin biopsies significantly reduced the number of postoperative wound infections.[18]

The effect of a smoking cessation intervention before surgery has also been evaluated previously in a few randomized clinical trials. Smoking cessation initiated 6 to 8 weeks before elective hip and knee arthroplasty has been shown to reduce the postoperative complication rate by 65%.[19] In contrast, preoperative smoking cessation for 1 to 3 weeks did not seem to influence the complication rate after colorectal surgery.[20] Some other observational studies have demonstrated positive effects for a preoperative smoking cessation period of 4 weeks or more.[21,22]

In summary, there is insufficient evidence concerning how the duration of smoking cessation affects the frequency of postoperative complications.[23,24] Our a priori hypothesis was that smoking cessation intervention, starting 4 weeks before surgery, reduces the risk of postoperative complications. To evaluate this, we performed a randomized trial investigating if an intervention of smoking cessation starting 4 weeks before general and orthopedic surgery would reduce the frequency of overall postoperative complications. The

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second objective was to evaluate the effect of smoking cessation on wound complications.

METHODS

Study Setting

This study was a randomized clinical trial conducted at 4 university-affiliated hospitals in the Stockholm capital region, Sweden. The study was planned according to the International Conference on Harmonisation Guidelines for good clinical practice, and the study was approved by the Ethics Committee of the Karolinska Institute (Ref. No. 03-214, 215) Stockholm and registered at Clinicaltrials.gov (ID NCT00533000).

Patients

Patients scheduled for primary inguinal and umbilical hernia repair, laparoscopic cholecystectomy, or a hip or knee prosthesis were asked to participate in the study. To be eligible, patients had to be daily smokers (>2 cigarettes daily for at least 1 year before inclusion) and aged 18 to 79 years. Patients with overt alcohol or drug abuse, pregnancy, severe mental illness, dementia, and poor Swedish language proficiency were excluded.

Assignment

Patients were enrolled after giving their informed consent by study nurses in the hospitals or by the treating surgeons, none of whom took part in the randomization procedure.

Randomization was done on the day of inclusion by the nurse administrating the smoking cessation intervention. Patients were randomized in a 1:1 ratio to a control group or intervention group, using opaque, sealed envelopes in blocks of 10, stratified by type of surgical procedure and clinic. The allocation was blinded to the treating surgeon, study nurses evaluating outcomes, and other medical staff.

Intervention

The intervention was intended to start 4 weeks before surgery and last 4 weeks after surgery, as described in detail elsewhere. The intervention included weekly meetings or telephone counseling with a nurse professionally trained in smoking cessation therapy, the telephone number to a hot line providing smoking cessation advice, and free nicotine substitution (Nicorette) offered with an individual schedule for the entire intervention period. No bupropion or varenicline was offered. Nicotine replacement therapy was the only drug offered. The intervention was aimed at keeping patients completely smoke-free from 4 weeks preoperatively until 4 weeks postoperatively. The control group received standard care, which, besides the neutral information given in the consent form, included little or no information about smoking cessation or the potential harm of tobacco smoking.

Baseline Data

Each patient filled out a questionnaire upon inclusion providing background information on marital status, occupation, and education level. The average alcohol consumption per week was recorded and the previous smoking history was categorized in pack years. The Fagerström score[25] was used to measure nicotine dependency. Information on regular exercise and body mass index (BMI) was recorded. A preoperative health evaluation determined the ASA class,[26] forced expiratory volume (FEV 1,0), the presence of comorbidities and any medications. The smoking status of all participants was evaluated preoperatively both by self-administered questionnaires and measurements of carbon monoxide (CO) in the expired air (Micro Smokerlyzer; Bedfont Scientific Ltd, Rochester, UK).

Follow-up Data

Each patient answered a self-administered structured questionnaire about smoking habits and underwent a repeated CO measurement at follow-up at the clinic 2 to 3 weeks postoperatively. For the intervention group, smoking status and tobacco consumption were recorded each week during the intervention. In the per protocol analysis, patients were divided into 3 groups. Patients were judged successful in smoking cessation if they reported smoking zero cigarettes for the minimum period of 3 weeks before surgery until 4 weeks postoperatively and if the postoperative level of exhaled CO was ≤10 parts per million (ppm). The second group consisted of patients that reported smoking zero cigarettes for the period of 1 to 2 weeks before surgery until 4 weeks postoperatively, with a postoperative CO of ≤10 ppm. The last group was those who continued to smoke or only reduced smoking.

Outcome Measures

The main outcome measure was the frequency of any postoperative complication within 30 days. The secondary outcome was the frequency of any wound complication during the same follow-up period. Complications were recorded by the study nurse at the 2- to 3-week clinical follow-up and also via a telephone interview at 4 weeks postoperatively. Complications were predefined in the study protocol (Table 1), and all study nurses were given the same information and training on how to record possible complications on the case record form (CRF). Each complication recorded in the study protocol by the study nurse was also double-checked by the authors reviewing the medical record. A complication was defined as any unexpected event causing additional medical or surgical treatment, additional investigations (radiography, laboratory tests), a prolonged hospital stay, or unscheduled postoperative check-ups at the outpatient department. The study physicians evaluated all complications without knowledge of group allocation. This was arranged as a panel discussion to reach consensus on status of each possible complication without prior knowledge of the particular group allocation. For this discussion, information on all complications registered by the study nurses was available as was all information in the medical records.

Power Calculation

The power calculation was based on the results of previous randomized trials[18,19] and was performed with a 2-tailed test. We made a conservative estimate of a baseline complication rate of 30% and a treatment effect of 30%

TABLE 1. Prespecified Definitions of Postoperative Complications

Wound complications
Seroma (wound revision, wound drainage or need for repeated wound dressings)
Superficial wound infection (infection treated with antibiotics or repeated wound dressings)
Deep wound infection (treated with surgical debridement)
Hematoma (treated with surgical intervention, blood transfusion, or extra wound checks)
Wound dehiscence (redo surgery)
Skin necrosis (surgical wound revision or repeated wound checks)
Pressure wounds (wound revision or need for repeated wound dressings)
Urinary tract complications
Urinary retention (need of catheterization after surgery)
Urinary tract infection (treated with antibiotics)
Renal failure (oliguria <500 mL/24 h or increase in creatinine with more than 30%)
Gastrointestinal complications
Intolerance to po nutrition and prolonged need of iv fluids (>24 h)
Small bowel obstruction (redo surgery or gastrointestinal x-ray series)
Biliary leakage (redo surgery or endoscopic retrograde cholangiography)
Pulmonary complications
Pneumonia or bronchitis (treated with antibiotics)
Respiratory insufficiency (postoperative need of ventilator support, postoperative need for oxygen more than 24 h or other respiratory treatments)
Cardiovascular complications
Myocardial infarction/angina pectoris/heart failure/arrhythmias (causing treatment, prolonged observation or additional diagnostic work-up)
Stroke/TIA (neurological symptoms causing treatment, prolonged observation or additional diagnostic work-up)
Deep venous thrombosis (treated and verified with duplex or phlebography)
Pulmonary embolism (treated and verified with computerized tomography)
Other infectious complications
Fever of unknown origin (treated with antibiotics or additional investigations)
Sepsis (blood borne infection treated with antibiotics)
Prosthesis related
Fracture of prosthesis (x-ray verified)
Dislocation of prosthesis (x-ray verified)
Peripheral nerve injury (clinical or neurophysiologic diagnosis)
Other
Redo surgery (cause)
Death (cause)
Other complication (specify)
Any complication (yes/no)

reduction of complications. We planned to include 586 patients in total to identify a 30% reduction (from 30% down to 21%) in the complication rate with a statistical power of 80% ($\beta = 0.20$) at the significance level of 0.05 (α). The inclusion was terminated in December 2006 before the estimated number was met since recruitment was slowing down. No interim analysis was done.

Statistics

Primary analyses were performed according to intention-to-treat and secondary analyses were performed using per protocol information. Fisher exact test was used for dichotomous data and Mann-Whitney when applicable. The level of statistical significance was set at $P < 0.05$ and tests were always 2-sided. We also calculated the absolute and relative risk reduction and the numbers of patients needed to treat (NNT).

Because of the that the estimated number of patients in the power calculation was not met, further analyses were also done. We used binomial logistic regression to study potential confounders due to the differences between the 2 groups at baseline. First, a univariable analysis with randomization status as the only explanatory variable was introduced. Parameter estimate was assessed with Wald's test. Secondly, each additional variable at baseline (Table 2) was added to

TABLE 2. Baseline Characteristics

	Control Group (n = 54)	Intervention Group (n = 48)
Main characteristics		
Age, median (IQR)*, yr	57.5 (49–64)	55 (46–60)
Female sex, No. (%)	30 (56)	18 (38)
Body mass index, median (IQR), kg/m^2	25 (23–29)	26 (24–30)
ASA class 1 or 2, No. (%)	46 (85)	44 (92)
ASA class 3 or 4, No. (%)	8 (15)	4 (8)
Current diseases		
Diabetes, No. (%)	2 (4)	0 (0)
Hypertension, No. (%)	11 (20)	8 (17)
Chronic heart disease, No. (%)	8 (15)	1 (2)
Chronic obstructive pulmonary disease or asthma, No. (%)	6 (11)	6 (13)
Preoperative laboratory test		
Hemoglobin, median (IQR), g/L, (n = 100)	142 (134–153)	144 (134–153)
FEV_1, median (IQR), L/s, (n = 99)	2.5 (2.0–3.2)	2.5 (2.2–3.5)
Smoking data		
Cigarettes per day, median (IQR)	15 (10–20)	15 (10–20)
Years of smoking, median (IQR), yr	36.5 (30–45)	34.5 (25–42)
CO in exhaled air, median (IQR), (n = 101)	14 (8–20)	15.5 (8–22)
Type of surgery		
Hernia surgery, No. (%)	17 (32%)	21 (44%)
Laparoscopic cholecystectomy, No. (%)	18 (33%)	9 (19%)
Hip replacement, No. (%)	15 (28%)	10 (21%)
Knee replacement, No. (%)	4 (7%)	8 (17%)
Perioperative data		
Duration of surgery, median (IQR), min	73.5 (50–95)	80 (61–102)
Preoperative antibiotics, No. (%)	29 (54%)	25 (52%)
Day care surgery, No. (%)	8 (15%)	16 (33%)
Surgeon in training, (resident), No. (%)	14 (26%)	14 (29%)

*Interquartile range.

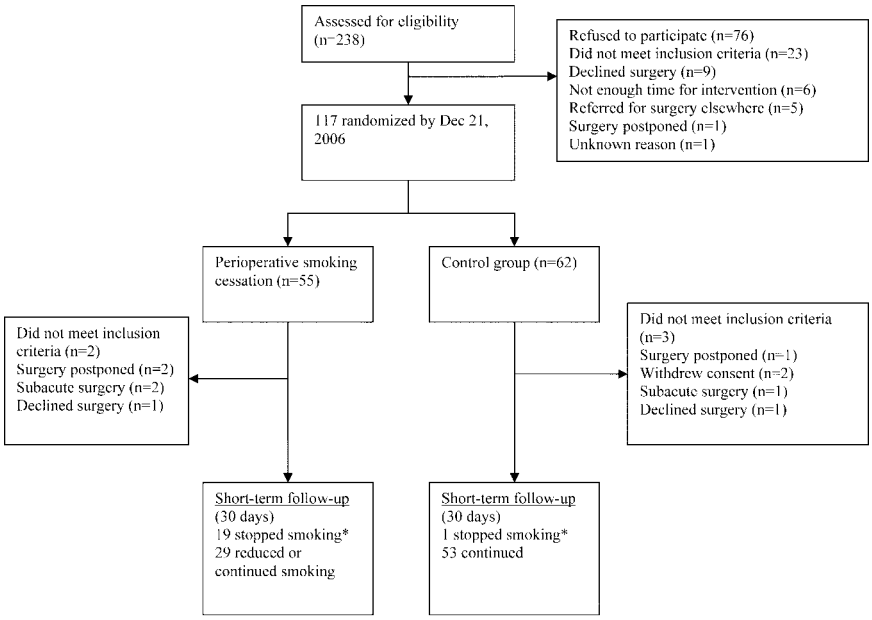

FIGURE 1. Trial profile.

the model one at a time. A variable was a priori considered to be a confounder if the relative risk (RR) for randomization status changed by more than 10% when the new variable was added to the model. Data were analyzed in SPSS version 15.0 (SPSS, Chicago, IL).

RESULTS

Patient Enrollment

Between February 16, 2004, and December 21, 2006, a total of 117 patients were enrolled in the study. The follow-up for the primary outcome was completed March 5, 2007. There were no losses to follow-up, but 7 patients in the intervention group and 8 patients in the control group were not included in the analysis; no patient in the intervention group discontinued intervention. Five patients were incorrectly randomized because they did not meet the inclusion criteria (pipe smoker, cheroot smoker, bilateral hip prosthesis, bilateral knee prosthesis, and recurrent hernia). In total, 102 patients remained for analysis, for details see CONSORT flow chart in Figure 1. There was only 1 patient in the control group (2%) who stopped smoking for the entire study period, compared with 19 (40%) in the intervention group ($P < 0.001$).

Baseline Characteristics

Baseline demographics are presented in Table 2. The mean age was 55 years and 53% (n = 54) were men. Baseline smoking data are equal in the 2 groups, and current diseases are slightly unevenly distributed due to the low number of participants with diseases. The majority (64%) underwent a general surgery procedure and 36% an orthopedic surgery procedure. The frequency of complications in different types of surgery is shown in Table 3. Hernia procedures had the highest complication rates (42%), compared with knee prosthesis (33%), hip prosthesis (24%), and laparoscopic cholecystectomy (22%). These differences between the types of surgical procedures were not significant ($P = 0.29$).

TABLE 3. Postoperative Complications According to Type of Surgery

	Any Complication No. (%)	*P*
Hernia surgery (n = 38)	16 (42%)	
Hip prosthesis (n = 25)	6 (24%)	0.29*
Knee prosthesis (n = 12)	4 (33%)	
Laparoscopic cholecystectomy (n = 27)	6 (22%)	
Total (n = 102)	32 (31%)	

*χ^2 test of the difference in complication rate between different types of surgery.

Intention-to-Treat Analysis

The outcome according to intention to treat is presented in Table 4. The overall complication rate in the intervention group was significantly reduced compared with the control group, 21% and 41% ($P = 0.03$), respectively. The relative risk for the primary outcome of any postoperative complication in the intervention group was 0.51 (95% confidence interval (CI), 0.27–0.97), and the number needed to treat was 5 (95% CI, 3–40). The secondary outcome wound complication rate was 13% in the intervention group and 26% in the control group ($P = 0.13$). The relative risk for the secondary outcome of any wound complication in the intervention group was 0.48 (95% CI, 0.20–1.16). The small numbers in each subgroup of complications prevent further meaningful analyses of these data. No adverse events related to intervention were observed.

TABLE 4. Intention to Treat Analysis. Postoperative Complications Within 30 Days and Hospital Stay

	Intervention Group (n = 48)	Control Group (n = 54)	Relative Risk (95% CI)	*P**
Hematoma, No. (%)	3 (6)	7 (13)		0.33
Wound infection, No. (%)	2 (4)	4 (7)		0.68
Seroma, No. (%)	3 (6)	5 (9)		0.72
Other wound complication, No. (%)	2 (4)	4 (7)		0.68
Any wound complication, No. (%)	6 (13)	14 (26)	0.48 (0.20–1.16)	0.13
Urinary tract complication, No. (%)	4 (8)	9 (17)		0.25
Pulmonary complication, No. (%)	0 (0)	1 (2)		1.00
Cardiovascular complication, No. (%)	1 (2)	1 (2)		1.00
Gastrointestinal complication, No. (%)	3 (6)	0 (0)		0.10
Fever of unknown origin, No. (%)	0 (0)	1 (2)		1.0
Any complication, No. (%)	10 (21)	22 (41)	0.51 (0.27–0.97)	0.03
Hospital stay (d) (median, min-max)	1, 0–10	1, 0–11		0.23†

*Fisher exact test (2-sided), if not stated otherwise.
†Mann-Whitney (2-sided).

TABLE 5. Per Protocol Analysis. Postoperative Complications Within 30 Days in Relation to Perioperative Abstinence Period

	Stopped Smoking ≥3 Week Preoperatively* (n = 20)	Stopped Smoking 1 to 2 Week Preoperatively† (n = 9)	Continued Smoking (n = 73)	*P*
Any wound complication, No. (%)	2 (10)	0 (0)	18 (25)	0.10‡
Any complication, No. (%)	3 (15)	2 (22)	27 (37)	0.14‡

*Abstinence defined by smoking zero cigarettes for a minimum period of 3 week before surgery until 4 week postoperatively and postoperative carbon monoxide ≤10 ppm.
†Abstinence defined by smoking zero cigarettes for a period of 1 to 2 week before surgery until 4 week postoperatively and postoperative exhaled carbon monoxide level ≤10 ppm.
‡χ^2 (2-sided).

Per Protocol Analysis

Complications were also evaluated according to smokers who stopped ≥3 weeks preoperatively, 1 to 2 weeks preoperatively, and those who continued smoking. The frequencies of any complication according to the analysis per protocol were 15%, 22%, and 37%, respectively ($P = 0.14$; Table 5). In this analysis, patients were judged successful in smoking cessation only if they reported smoking zero cigarettes from the respective preoperative period to 4 weeks postoperatively. This strict definition of a successful cessation led to only 20 patients being analyzed as nonsmokers for the whole study period. The trend of the effect seen in per protocol analysis was almost the same as in the intention to treat analysis. The self-reported quit-smoking rate was supported by the measurement of CO in exhaled air: abstainers exhaled 1.0 ppm (0–10) on a median and the corresponding value for those who reduced or continued their smoking was 9.0 ppm (0–35) ($P < 0.001$).

Binomial Regression Analysis

A binomial logistic regression analysis did not show any confounding effects on the results, explained by the differences between the 2 groups seen at baseline in Table 2. Regression modeling was performed only on the intention to treat analysis and with the primary outcome of any postoperative complication. The relative risk (RR) of being in the intervention group as the only explanatory variable in the model was 0.51 (95% CI, 0.27–0.97; $P = 0.04$). None of the variables at baseline affected the RR of 0.51 by more than 10% in either direction and no further analysis was done.

DISCUSSION

This study shows that perioperative smoking intervention initiated as late as 4 weeks before elective surgery reduces the risk of postoperative complications. This is an important finding for patients undergoing surgical procedures for diagnoses that do not allow the 6 to 8 weeks of smoking cessation that have previously been shown to be effective in reducing complication rates. This finding is in line with previous trials,[18,19] but the effect has not been demonstrated in a clinical trial for such a short preoperative time frame.

The per protocol analysis supports the effect of abstinence per se in reducing complication rates, but these data must be interpreted with caution considering the low statistical precision and the nonrandomized nature of the data. The finding, although not statistically significant, that those who really were abstinent throughout the whole study period had

fewer complications, suggests that there is a causal connection between abstaining and fewer complications. The strong effect of smoking cessation could partly be explained by a higher oxygen delivery to the healing tissues. This hypothesis is supported indirectly by the positive effect seen with supplementary oxygen delivery.[27,28] Smoking also alters the immune system,[29] and the elevated levels of white blood cells has previously been shown to be a reversible condition.[30] The proportion of abstinent individuals in the whole intervention group increased from 40% 3 weeks before surgery to 58% the week before surgery. This efficacy of the intervention in achieving successful abstainers is comparable to the result reported by Moller et al[19] The reason we chose counseling and NRT for the intervention was that this is the only evidence-based therapy for preoperative smoking cessation. Our intervention was more effective than that observed in some low-intensity protocols[31] not using repeated personal contacts and NRT for the whole study period. The relatively high probability of successful smoking cessation might reflect the motivating effects of surgery.[32] Smoking cessation therapy seems to be more efficient when introduced before a surgical procedure, and the preoperative period might therefore represent a golden moment for smoking cessation. Comparing the quit rates in the Cochrane reports from preoperative smoking cessation intervention[23] with other smoking cessation interventions[33–35] supports this theory. Smoking cessation also has general health benefits that reach far beyond the perioperative period[36] and smoking cessation with nicotine replacement therapy and counseling have previously been proven to be cost-effective.[37,38]

The strength of our study is, besides the randomized nature of the data, the blinded outcome assessment and rigorous follow-up. It is also unique in that it is the first randomized trial investigating a preoperative smoking cessation period of 4 weeks. We believe the generalizability to be high because we have included a wide spectrum of surgical procedures and ages and tried to minimize exclusion criteria.

Some limitations of this study are worth discussing; first the frequency of patients who declined participation may affect the external validity. In our attempt to reduce the refusal rate, we tried different approaches to patients during the process of inclusion. Nevertheless, we still found a significant proportion of patients who were not interested in smoking cessation. Common reasons for refusal that were given included no interest in giving up smoking or a need to focus on the forthcoming surgical procedure. The relatively small number of patients may also increase the risk of a type II error, overlooking other possible effects of the intervention. Especially the impact on our secondary outcome, wound complications, may have suffered from the limited sample size because the relative size of the effect was as strong as we expected. In the study base of the Stockholm region, the prevalence of daily smokers has steadily decreased down to a unique low 15% during the end of our study period.[39] Smoking also has a sociodemographic distribution where immigrants smoke in a higher proportion than Swedish-born nationals and alcohol abuse is also more common among smokers. These last 2 factors contributed to our difficulties in finding smokers that met our inclusion criteria. During our planning of time needed for inclusion, these factors and the refusal rate were underestimated.

Our relatively high rate of postoperative complications (31%) might be a result of our definition of a complication (ie, any unexpected event that necessitates treatment, extra investigation, or prolonged care) and a rigorous follow-up. This wide definition should not weaken the results because the same criteria for a complication were used in both groups, so any misclassification is most likely nondifferential. Minor complications may still have a significant impact on health-economic evaluations. Major complications influence not only the in-hospital care but also decreases long-term survival.[40] Our definitions of complications are partly based on the work by Bennett-Guerrero et al[41] who also found complication rates higher than what is often reported. The reason for this is that the definitions also include less severe forms of morbidity, which are often overlooked but still can have important impact. One must also consider that all patients in the study are daily smokers with a higher baseline risk than a mixed population, and the previous trial by Moller et al[19] also found a high baseline complication risk.

There is a possible information bias due to the fact that the blinding of the outcome assessors may not have been perfect. Some of the patients might have revealed their randomization status so that the assessor looking for complications might have been biased. To avoid this possible bias, the study physicians arranged panel discussions to reach a consensus on each complication without prior knowledge of the particular group allocation. Furthermore, the study nurses may have recorded complications differently. We tried to avoid this by training and by giving the same information to all of them and also by having written, prespecified definitions of possible complications.

In conclusion, perioperative smoking cessation seems to be an effective means of reducing postoperative complications even when introduced as late as 4 weeks before surgery. The potential impact of even shorter periods of perioperative smoking cessation intervention remains to be tested since this trial was not designed to answer that question.

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