

Effect of propofol and sevoflurane on coughing in smokers and non-smokers awakening from general anaesthesia at the end of a cervical spine surgery

P. Hans*, H. Marechal and V. Bonhomme

University Department of Anaesthesia and Intensive Care Medicine, CHR de la Citadelle, Bd du 12eme de Ligne, 1, 4000 Liege, Belgium

*Corresponding author. E-mail: pol.hans@chu.ulg.ac.be

Background. Coughing during emergence from general anaesthesia may be detrimental, particularly after cervical spine surgery. We compared the effect of propofol or sevoflurane anaesthesia on the incidence and severity of coughing during recovery in patients undergoing cervical spine surgery via an anterior approach. As a secondary aim, we also evaluated the influences of smoking and estimated residual anaesthetic agent concentrations on coughing.

Methods. Thirty-four patients were enrolled in a randomized prospective, double-blind study to receive either propofol (PPF) or sevoflurane (SEVO) for maintenance of anaesthesia. The decision to perform tracheal extubation was based on specified criteria, including resumption of spontaneous respiration and consciousness. During emergence from anaesthesia and extubation, coughing was observed and graded at predefined times.

Results. The incidence of severe coughing was higher in the SEVO group than in the PPF group (59% and 6%, respectively), and also in smokers than in non-smokers (50% and 17%, respectively). The peak incidence of coughing was at tracheal extubation. The probability of coughing was influenced by the estimated residual concentration of anaesthetic agents at extubation, except for smokers in the SEVO group who were at the highest risk of coughing.

Conclusions. The incidence of coughing after cervical spine surgery when tracheal extubation is performed according to clinical criteria is lower after propofol anaesthesia compared with sevoflurane anaesthesia. Smokers are at increased risk of coughing, independently of the type of anaesthesia maintenance. Higher residual concentrations of anaesthetic agents decrease the probability of coughing, except for smokers anaesthetized with sevoflurane.

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Coughing during emergence from general anaesthesia may cause a number of potentially detrimental effects, including severe cough, laryngospasm, and cardiovascular disturbances, and also increases in intracranial intraocular, and intra-abdominal pressures. In patients undergoing cervical spine surgery, it may also cause bleeding or displacement of a bone or synthetic graft which may cause acute airway obstruction or neurological injury. Hence, one of the main objectives of anaesthetic management in these patients is to avoid coughing during emergence from anaesthesia.

Several different drugs and techniques have been investigated to prevent coughing during emergence from

anaesthesia and tracheal extubation. These strategies include the use of a laryngeal mask instead of a tracheal tube,¹ extubation at a deep level of anaesthesia,² the systemic administration of drugs such as short-acting opioids,³ dexmedetomidine,⁴ and local anaesthetics,⁵ or the application of local anaesthetics and steroids inside or around the cuff of the tracheal tube.^{6–8} None of these can guarantee total absence of coughing.

Hypnotics differently affect airway reflexes. Propofol has been shown to preserve airway integrity and inhibit laryngospasm,^{9 10} although this beneficial effect has not been confirmed.¹¹ Sevoflurane does not elicit cough reflexes and

is considered as the least irritant halogenated anaesthetic agent.¹² Total i.v. anaesthesia was recently reported to be associated with less coughing and reduced haemodynamic responses upon emergence, compared with balanced anaesthesia.¹³ However, in this study, the two groups of patients differed not only by the hypnotic agent but also by the opioid regimen and the gas mixture used for artificial ventilation. Furthermore, regardless of the type of anaesthesia, the role of smoking as an additional risk factor of coughing during emergence remains controversial.^{14 15}

The aims of this study were to determine the incidence of coughing during emergence from cervical spine surgery in patients anaesthetized using either propofol (PPF) or sevoflurane (SEVO) for maintenance of anaesthesia. A secondary aim was to determine the severity and moment of occurrence of those coughing episodes during the course of recovery and to examine the influence of a smoking history and residual concentrations of anaesthetic agents on the incidence of coughing.

Methods

After Institutional Ethics Review Board approval and informed consent, 34 ASA status I or II patients undergoing cervical spine surgery via an anterior approach were recruited for this prospective randomized double-blind study. Patients with a history of recent respiratory infection, asthma, chronic pulmonary disease or coughing, signs of a possible difficult intubation, pregnancy, and alcohol or drug abuse were excluded from the study. Patients were considered as smokers when they had a history of smoking at least five cigarettes a day for more than 6 months in the period before surgery.

Premedication comprised alprazolam 0.5 mg and atropine 0.5 mg orally 1 h before surgery. Upon arrival in the operating theatre, non-invasive arterial pressure monitoring, ECG, and pulse oximetry were instituted in all patients (Datex-Ohmeda S/5TM, Helsinki, Finland). Neuromuscular transmission was monitored at the wrist by accelography and assessed using the train-of-four stimulation mode (TOF-Watch monitor, Organon Tenika BV, Boxtel, The Netherlands). Depth of anaesthesia was monitored with the Datex-Ohmeda S/5 Entropy Module (M-EntropyTM) using a specific entropy sensor (Datex-Ohmeda Division, Instrumentarium Corporation, Helsinki, Finland). On the basis of the chronological order of their admission for surgery, and using a computer-generated randomization list, patients were randomly allocated to one of the two groups according to the hypnotic agent used for anaesthesia maintenance. The randomization did not take into account smoking habits of patients. In the PPF group, anaesthesia was induced and maintained using a propofol target-controlled infusion (PPF TCI, model of Marsh, DiprifusorTM, Alaris Medical System, Basingstoke, UK). In the SEVO group, anaesthesia was

induced with a 2 mg kg⁻¹ bolus of propofol i.v. and maintained with sevoflurane. In both groups, patients received a target-controlled remifentanyl infusion to achieve an effect-site concentration between 3 and 5 ng ml⁻¹ (Alaris PK MK3, model of Minto, Alaris Medical System, Basingstoke, UK) that was continuously adjusted to meet anti-nociceptive requirements according to surgical events. Propofol target concentration and sevoflurane concentration were continuously adjusted to keep the state entropy value between 40 and 50 during the procedure. After muscle relaxation was obtained with a bolus dose of cisatracurium (0.15 mg kg⁻¹), high volume–low pressure cuff tracheal tubes of 7.5 mm inner diameter for women and 8.5 mm diameter for men were sited by a senior anaesthesiologist. The cuff was inflated with air to achieve a cuff pressure of 15 mbar. Patient's lungs were ventilated with an air/oxygen mixture ($F_{I_{O_2}}$: 0.5) to maintain end-tidal CO₂ partial pressure 4.5 kPa. An additional dose of cisatracurium 0.03 mg kg⁻¹ was given before skin incision, after which the return to a normal neuromuscular function was checked during the surgical procedure.

One hour before the end of surgery, all patients received 2 g of acetaminophen i.v. for postoperative analgesia.¹⁶ To ensure that no premature coughing episode would occur before the end of the procedure in our non-paralysed patients, remifentanyl and propofol or sevoflurane were discontinued simultaneously at the very end of skin closure. Patients were administered oxygen 100% and allowed to breathe spontaneously. After resumption of regular spontaneous respiration, the ability to respond to verbal commands was regularly assessed in the absence of any other external stimulation and patients were extubated when capable to open their eyes on command. These clinical criteria were mandatory for the anaesthesiologist to remove the tracheal tube. During emergence, coughing was observed and graded at different time points by the same anaesthesiologist blinded to the study protocol and the anaesthesia regimen, who entered the operating theatre at the time of cessation of anaesthetic agents. Patient monitor screen and syringes were hidden to the blinded observer, and he was also kept at distance from the patient in order to prevent him from smelling sevoflurane. Data were recorded at occurrence of first spontaneous breath (FB), resumption of regular spontaneous ventilation (RB), ability to respond to verbal command ('open your eyes') (VC), cuff deflation (CD), extubation (EXT), and 2 min after extubation (EXT+2). Severity of coughing was graded using a four-level scale adapted from the scale of Minogue and colleagues.⁶ Grade 0 corresponded to no cough, Grade 1 to light (single) cough, Grade 2 to moderate cough (more than one episode of non-sustained coughing), and Grade 3 to sustained and repetitive cough movements with head lift. Estimated effect-site propofol and remifentanyl concentrations and end-tidal sevoflurane concentration were also recorded immediately before tracheal extubation. The emergence time was recorded as the

time elapsed between stopping administration of anaesthetic agents and extubation.

Data analysis and statistics

Initial sample size calculation was based on a global coughing incidence of 66%, as reported by Olympio and colleagues.¹⁷ On the basis of a 50% clinically relevant reduction in that incidence, and an alpha level of 0.05, a total sample size of 33 is needed to achieve a power of 80%.

Data were expressed as mean (SD) or per cent counts unless otherwise indicated. Data were compared using χ^2 tests or Fisher's exact tests for proportions and two-tailed unpaired *t*-tests for continuous variables. A *P*-value of <0.05 was considered statistically significant. The probability of no Grade 2 or 3 cough as a function of residual remifentanyl concentration and propofol or sevoflurane concentration at extubation was calculated in smokers and non-smokers using multinomial logistic regression with SPSS[®] software (version 16.0, SPSS Inc., Chicago, IL, USA). The independent variables (covariates) were the residual estimated effect-site concentration of remifentanyl (Ce-remi) at the time of extubation, the estimated effect-site concentration of propofol (Ce-PPF), the end-tidal concentration of sevoflurane (ETsevo) at the same time, and the subgroup of patients (categorical variable) (SEVO-non-smoker, SEVO-smoker, PPF-non-smoker, and PPF-smoker). The dependent variable was the probability of no Grade 2 or 3 cough at extubation. The software estimates the parameters *a*, *b*, *c*, *d*, *e*, *f*, and *g* that fit best the equation $\text{logit}(P) = \ln [P/(1-P)] = a + b(\text{Ce-remi}) + c(\text{Ce-PPF}) + d(\text{ETsevo}) + e x + f y + g z$. In this equation, *P* is the probability of no Grade 2 or 3 cough at extubation, *x*=1 for SEVO-non-smoker and 0 for the other categories, *y*=1 for SEVO-smoker and 0 for the other categories, and *z*=1 for PPF-non-smoker and 0 for the other categories. Parameters are provided with standard errors (SE). A Nagelkerke pseudo-*R*² test is a logistic analogy to the *R*² provided by classical least square regression, but it is not equivalent. It estimates the strength of the relationship between the studied variables. A Nagelkerke pseudo-*R*² ranging between 0.2 and 0.4 is considered satisfactory. Pearson and deviance χ^2 tests provide a χ^2 value and a probability. They test the null hypothesis that the model adequately fits the data. If this probability is higher than 0.05, the above-mentioned null hypothesis cannot be rejected, implying that the model fits the data at an acceptable level. Overall per cent of accurate prediction by the model is also given by the software.

Results

The two groups were comparable with respect to patient characteristics and proportion of smokers (Table 1). The incidence of at least one episode of severe coughing

Table 1 Patient characteristics, and mean time between stopping anaesthetic agents and extubation (emergence time), and residual remifentanyl effect-site concentration (remifentanyl). Data expressed as mean (SD or range) or number. * *P*=0.03; ** *P*=0.001

	SEVO	PPF
Age (yr)	44 (29–58)	49 (39–64)
Weight (kg)	77 (18)	71 (17)
Height (cm)	170 (8)	170 (9)
Gender (male/female)	10/7	9/8
ASA (I/II)	10/7	6/11
Smokers/non-smokers	7/10	9/8
Emergence time (min)	12 (3)	9* (4)
Effect-site remifentanyl concentration (ng ml ⁻¹)	0.71 (0.45)	1.54** (0.66)

(Grade 3) was significantly higher in patients anaesthetized with sevoflurane than in those anaesthetized with propofol [10/17 (60%) and 1/17 (6%), respectively; *P*=0.001], and higher in smokers than in non-smokers [8/16 (50%) and 3/18 (17%), respectively; *P*=0.04]. Details regarding the proportion of each grade of cough in each group of patients are given in Figure 1. In the PPF group, 0/48 (0%) and 1/54 (3%) Grade 3 coughing episodes were recorded in non-smoking and smoking patients, respectively. Conversely in the SEVO group, 27/42 (64%) coughing events recorded in smoking patients were of Grade 3, and the corresponding number was 8/60 (13%) in non-smoking patients. The incidence of severe coughing was maximal at the time of extubation, since 9/34 (26%) and 11/34 (32%) of coughing events were of Grade 3 at the time of cuff deflation and extubation, respectively (Fig. 2), as opposed to 3/34 (9%), 5/34 (15%), 6/34 (18%), and 2/34 (6%) at first breath, regular breathing, response to verbal command, and during the first 2 min after extubation, respectively.

Mean (SD) emergence time was 9 (4) min in the PPF group and 12 (3) min in the SEVO group (*t*₃₂=2.26, *P*=0.03). The mean (SD) residual effect-site concentration of remifentanyl immediately before extubation was 1.54 (0.66) ng ml⁻¹ in the PPF group and 0.71 (0.45) ng ml⁻¹ in the SEVO group (*t*₃₂=4.22, *P*<0.001) (Table 1).

Multinomial logistic regression analysis allowed modelling the relationship between residual remifentanyl effect-site concentration, and propofol concentration or end-tidal sevoflurane concentration immediately before extubation on one hand, and the probability of no Grade 2 or 3 cough at the time of extubation on the other hand, in the PPF group (Fig. 3A), and also in the SEVO group (Fig. 3B) for smokers and non-smokers. The obtained model fitted the data at an acceptable level, as indicated by the Nagelkerke pseudo-*R*² value of 0.663, the Pearson $\chi^2_{(27)}$ statistic of 21.571 (*P*=0.759), and the deviance $\chi^2_{(27)}$ value of 20.917 (*P*=0.79). Percentage of accurate prediction was 82.4% for this model. Parameter estimates and SE are provided in Table 2. The effect of residual remifentanyl concentration was weak, as opposed to the effect of end-tidal sevoflurane concentration or effect-site propofol concentration. According to the model, and for a same residual effect-site

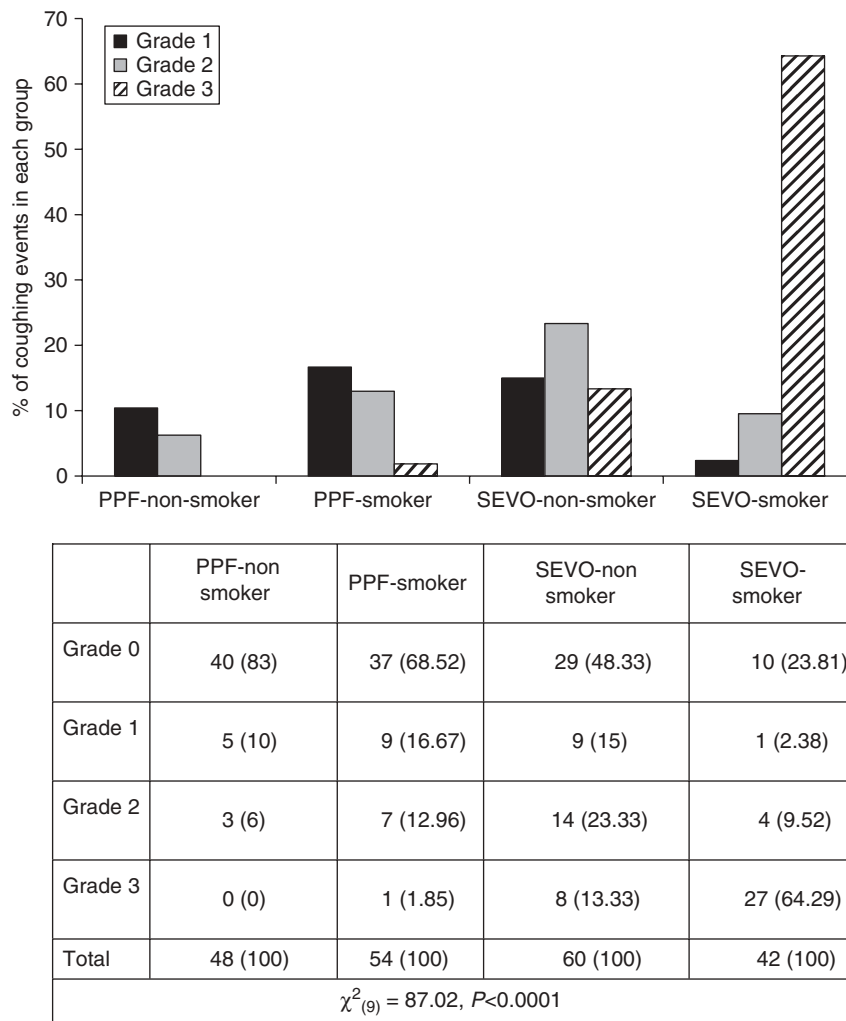


Fig 1 Occurrence of cough (Grades 1–3) in per cent of coughing events recorded in each group (PPF, SEVO, smokers, and non-smokers). The table provides the absolute recorded numbers and proportions [n =number of Grades 0, 1, 2, or 3 coughing events recorded, irrespective of the time point of interest (% , proportion of the total number of coughing events in the group)]. The results of the χ^2 test are also provided. PPF, propofol group; SEVO, sevoflurane group; Grade 0, no cough; Grade 1, light cough; Grade 2, moderate cough; Grade 3, severe cough.

concentration of propofol, the probability of Grade 2 or 3 cough at extubation is higher in smokers than in non-smokers. Conversely, in smoking patients of the SEVO group, the probability of grade 2 or 3 cough at extubation is extremely high (very close to 1) regardless of the residual end-tidal concentration of sevoflurane.

Discussion

In this study, we found that propofol anaesthesia reduced the incidence of coughing during emergence compared with balanced general anaesthesia with sevoflurane. This assertion must be moderated by the potential influence of residual concentrations of anaesthetic agents at the time of extubation, which may inhibit the cough reflex elicited by the mechanical effect of the tracheal tube on the larynx and the trachea. Although clinical criteria for extubation were met slightly earlier in the PPF group, the residual

concentration of remifentanyl at that time was significantly higher in the PPF group than in the SEVO group. Hence, when steering anaesthesia to achieve stable state entropy values and discontinuing hypnotic and opioid agents at the same time, a PPF–remifentanyl combination allows a slightly earlier clinical recovery compatible with extubation than a sevoflurane–remifentanyl combination. However, deeper residual anaesthetic effect in the PPF group could be responsible for the difference in the incidence of coughing. The logistic regression analysis indicates that propofol maintenance is only associated with a lower probability of coughing if propofol residual concentration is high enough at the time of extubation. According to the model, when residual propofol concentration decreases, the probability of coughing increases. This residual concentration dependence is also true when sevoflurane is used in non-smokers, and is in accordance with the results of Kim and Bishop,¹⁵ who demonstrated that

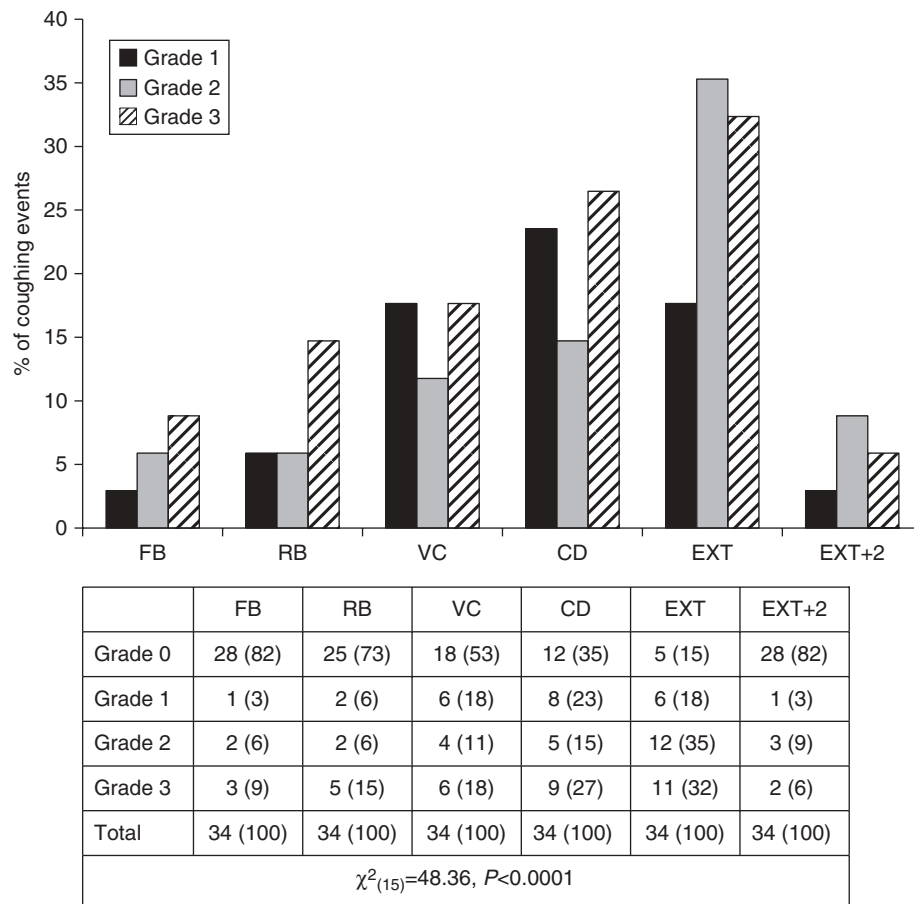


Fig 2 Coughing occurrence (Grades 1–3) in per cent at each time point of interest, all patients ($n=34$). FB, first spontaneous breath; RB, regular breathing; VC, response to verbal command; CD, cuff deflation; EXT, extubation; EXT+2, during the first 2 min after extubation. Similarly to Figure 1, the table provides the absolute numbers and the proportions. Grade 0, no cough; Grade 1, light cough; Grade 2, moderate cough; Grade 3, severe cough.

cough generally does not occur until the end-tidal isoflurane concentration is $<0.6\%$. Conversely, the effect of residual remifentanyl concentration on the probability of coughing is weak. Therefore, in order to decrease the risk of coughing, extubation should occur at a sufficient residual hypnotic agent concentration, provided that strict ventilatory and consciousness criteria are met at that time.

The moment of the highest coughing risk during emergence from anaesthesia has not been frequently addressed in the literature. In a study investigating the effects of smoking history on the amplitude and frequency of cough during emergence from isoflurane anaesthesia, it was noted that 52 out of the 68 enrolled patients (76%) coughed before responding to command.¹⁵ In the present study, this proportion was 15/34 (44%) when considering the whole sample of patients and coughing Grades 1, 2, or 3. It was 3/17 (18%) in Group PPF and 12/17 (71%) in Group SEVO. It is worth noting that this last incidence is similar to the one observed in patients anaesthetized with isoflurane.⁵

The present study also establishes that the incidence and the severity of coughing during emergence are significantly higher in smokers than in non-smokers. It is worth noting

that 7/7 of our patients with a history of smoking whose anaesthesia was maintained with sevoflurane exhibited a Grade 2 or 3 cough upon emergence, whereas the same cough grade was observed in 6/9 smokers who received propofol. In addition, logistic regression demonstrates that sevoflurane in smokers is associated with a 100% probability of coughing at extubation, whatever its residual concentration, and that at a same residual propofol concentration at extubation, smokers are at increased risk of coughing compared with non-smokers. These elements further support the assertion that smoking is associated with an increased risk of respiratory complications compared with non-smoking.¹⁸ Another study comparing airway responses during desflurane vs sevoflurane administration reported that cigarette smoking, but not the choice of the halogenated anaesthetic, placed patients at risk of respiratory complications including coughing.¹⁴ In contrast, in a study investigating cough during emergence from isoflurane anaesthesia, smokers were not more likely to cough than non-smokers.¹⁵ Other factors may theoretically influence the incidence and severity of coughing during emergence from general anaesthesia, such as a past medical history of asthma, chronic obstructive pulmonary

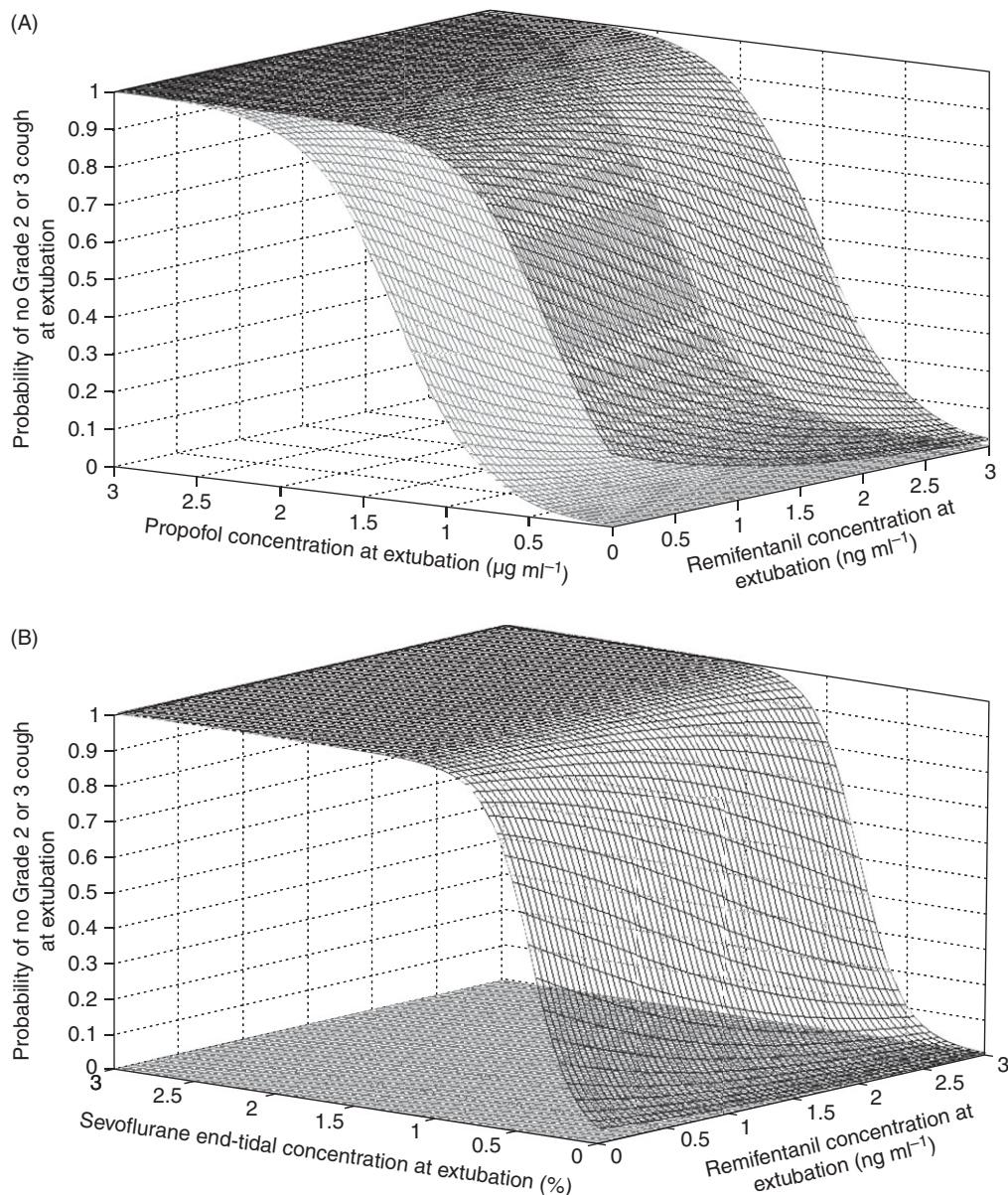


Fig 3 Surface–response curves illustrating the model obtained with the multinomial logistic regression analysis and corresponding to the probability of not observing Grade 2 or 3 coughing episodes as a function of residual anaesthetic agent concentration. (A) Surface–response curves when, in combination with remifentanil, propofol is the agent used for maintenance of anaesthesia in non-smokers (black surface) and in smokers (grey surface). (B) Surface–response curves when sevoflurane is the agent used in non-smokers (black surface) and in smokers (grey surface). Note that the probability of coughing is always equal to 1 in smokers anaesthetized with sevoflurane.

disease, recent airway infection, or chronic cough. Patients with these conditions were not included in this study, in an attempt to recruit homogeneous groups and to reduce potential confounding factors. However, these factors must be considered in individual patients.

In conclusion, in patients awakening from cervical spine surgery, coughing mainly occurs at the time of tracheal tube removal. Sevoflurane anaesthesia compared with propofol anaesthesia is associated with a significantly higher incidence and severity of coughing at extubation, when decision to remove the tracheal tube is based on strict

clinical criteria. The incidence and severity of coughing at extubation depend on the residual hypnotic agent concentration at that time, except for smokers anaesthetized with sevoflurane. Coughing at extubation is significantly more frequent and more severe in smokers than in non-smokers. Finally, smokers anaesthetized with sevoflurane are at very high risk of coughing at extubation, whatever the residual concentration of sevoflurane. Considering the potentially harmful complications of coughing during emergence from cervical spine surgery, total i.v. anaesthesia should be preferred in smokers in this particular setting.

Table 2 Parameter estimates and SE for the model obtained with the multinomial logistic regression analysis. The equation of the model is $\text{logit}(P) = \ln [P/(1-P)] = a + b(\text{Ce-remi}) + c(\text{Ce-PPF}) + d(\text{ET-sevo}) + e x + f y + g z$. The variable to which the parameter refers to is placed between brackets. See text for details

	Parameter estimates	SE
<i>a</i> (constant)	-5.069	3.566
<i>b</i> (Ce-remi)	-0.881	1.148
<i>c</i> (Ce-PPF)	3.927	2.672
<i>d</i> (ETsevo)	7.227	25.823
<i>e</i> (SEVO-non smoker)	1.927	7.853
<i>f</i> (SEVO-smoker)	-25.946	0.000
<i>g</i> (PPF-non smoker)	3.674	1.776
(PPF-smoker)	0	

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