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ORIGINAL ARTICLE

Emergence times and airway reactions during general anaesthesia with remifentanil and a laryngeal mask airway

A multicentre randomised controlled trial

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BACKGROUND Avoidance of airway complications and rapid emergence from anaesthesia are indispensable for the use of a laryngeal mask airway (LMA). Evidence from adequately powered randomised studies with a low risk of bias for the optimal anaesthetic in this context is limited.

OBJECTIVE We tested the hypothesis that when using remifentanil-based intra-operative analgesia, desflurane would be the most suitable anaesthetic: with noninferiority in the occurrence of upper airway complications and superiority in emergence times compared with sevoflurane or propofol.

DESIGN A randomised, multicentre, partially double-blinded, three-arm, parallel-group study.

SETTING Two university and two regional German hospitals, from February to October 2015.

PATIENTS A total of 352 patients (age 18 to 75 years, ASA physical status I to III, BMI less than 35 kg m^{-2} and fluent in German) were enrolled in this study. All surgery was elective with a duration of 0.5 to 2 h, and general anaesthesia with a LMA was feasible.

INTERVENTION The patients were randomised to receive desflurane, sevoflurane or propofol anaesthesia.

MAIN OUTCOME MEASURES This study was powered for the primary outcome 'time to state date of birth' and the secondary outcome 'intra-operative cough'. Time to emergence from anaesthesia and the incidence of upper airway complications were assessed on the day of surgery.

RESULTS The primary outcome was analysed for 343 patients: desflurane (n=114), sevoflurane (n=111) and propofol (n=118). The desflurane group had the fastest emergence. The mean (± SD) times to state the date of birth following desflurane, sevoflurane and propofol were 8.1 ± 3.6, 10.1 ± 4.0 and 9.8 ± 5.1 min, respectively ($P < 0.01$). There was no difference in upper airway complications (cough and laryngospasm) across the groups, but these complications were less frequent than in previous studies.

CONCLUSION When using a remifentanil infusion for intra-operative analgesia in association with a LMA, desflurane was associated with a significantly faster emergence and noninferiority in the incidence of intra-operative cough than either sevoflurane or Propofol.

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Introduction

Compared with an endotracheal tube, the laryngeal mask airway (LMA) facilitates general anaesthesia with a reduced risk of postoperative airway complications.[1] Desflurane's low solubility and minimal metabolism enable it to be a favourable anaesthetic agent for fast-track anaesthesia.[2] However, as regards upper airway complications, the use of desflurane with an LMA remains controversial.[2] In contrast to sevoflurane or propofol, desflurane induces a significant increase in respiratory resistance at 1.5 minimum alveolar concentration (MAC).[3] Furthermore, at one MAC anaesthetic levels desflurane is inferior to sevoflurane for the suppression of upper airway reactivity with tracheal stimulation.[4] Before launching this study, we performed a meta-analysis to assess the current evidence on emergence times and upper airway complications with the LMA, comparing desflurane with other volatile anaesthetics and propofol. We identified 13 randomised controlled trials.[5] The frequencies of intra-operative cough and laryngospasm and cough at emergence were high but comparable among all anaesthetics. Recovery times, that is the time to open the eyes, to remove the LMA, to respond to a command or to state the date of birth, were significantly shorter in the desflurane group than in the isoflurane, sevoflurane or propofol groups. However, the validity of previous trials was insufficient, and the abovementioned outcomes were mostly secondary endpoints. Moreover, cough at emergence was only analysed in two trials restricted to desflurane and sevoflurane, and laryngospasm at emergence was not analysed in any of the studies included. We also identified other issues with the included studies such as small sample sizes ($\leq$65 patients per group), strong interstudy heterogeneity and several studies used different amounts of anaesthetic and opioid across their study groups. All studies showed a high risk of performance bias and an unknown risk for selective reporting bias. Five studies revealed a high risk of detection bias.[6–10] Furthermore, previous studies were restricted to gynaecological,[11,12] urological[13,14] or orthopaedic surgery.[7–9] Thus, there is a need to address the issue of airway complications in an adequately powered study, ideally with a low risk of bias, and the inclusion of several types of surgery.

The current study was designed to verify the superiority of desflurane in terms of emergence times and to evaluate the occurrence of upper airway complications in patients when using an LMA along with remifentanil-based intra-operative analgesia. We hypothesised that compared with sevoflurane or propofol anaesthesia, the time to state the date of birth after desflurane anaesthesia would be superior (i.e. shorter) and that the incidence of intra-operative cough noninferior.

Methods

Study design

The prospective, multicentre, partially double-blinded, three-arm parallel-group, interventional randomised controlled study was conducted at two university hospitals (Aachen and Ulm) and two regional hospitals (Reutlingen and Halle) in Germany. Ethical approval (EK 314/14) was provided by the leading Ethics Committee of the University RWTH Aachen, Aachen, Germany (Chairperson Prof G. Schmalzing) on 15 January 2015. The study was registered at ClinicalTrials.gov (NCT02322502) and EudraCT (2014-003810-96). This study is reported in accordance with the CONSORT-Statement. A detailed study protocol has been published previously.[15] An extended summary of the methods is provided in Supplemental Digital Content 1, http://links.lww.com/EJA/A159. A brief summary is provided below.

Participants

Patients who met the inclusion criteria and were undergoing elective surgery under general anaesthesia, with an expected surgical duration of 0.5 to 2 h and in which the use of an LMA was feasible, were screened daily and enrolled in this study. These patients had an age of 18 to 75 years, ASA physical status I to III, a BMI less than 35 kg m^{-2}, were fluent in German and provided written informed consent. The main exclusion criteria were planned additional regional or local anaesthesia, severe pulmonary disease, psychiatric disorders or contraindications for the use of an LMA or any of the drugs administered in this study.

Randomisation and blinding

The patients were randomly assigned into one of the three groups (desflurane, sevoflurane or propofol) with an equal allocation ratio (1 : 1 : 1) according to a computer-generated randomisation sequence. This latter was based on the random allocation rule for the four centres (software framework 'R', The R Foundation for Statistical Computing, Vienna, Austria).[16] Only the responsible biostatistician had access to the randomisation sequence data. A patient's allocation was concealed in sequentially numbered, sealed opaque envelopes.

Our blinding procedure required two investigators for each randomised patient and is described in detail in the study protocol[15] and in Supplemental Digital Content 1, http://links.lww.com/EJA/A159.

Intervention

Briefly, patients received oral premedication with midazolam (3.75 to 7.5 mg). Anaesthesia was induced with a continuous intravenous infusion of remifentanil at 0.5 μg kg^{-1} over 60 s, followed by a titrated propofol injection of 1.5 to 2.5 mg kg^{-1}, before insertion of a LMA. The propofol was mixed with 20 mg lidocaine to mitigate injection pain.[17] Study centres were free to use their own preferred type of LMA, including first and second-generation LMAs: this enhanced the generalisability of the study, and avoided bias induced by unfamiliarity with one specific kind of LMA. Each LMA was

used according to the manufacturers' recommendations. The type of ventilation was not prescribed and neuromuscular blocking agents were avoided. According to the assigned intervention group, for anaesthesia maintenance, patients received either 4 to 5 vol.% end-expiratory desflurane, 1.2 to 1.4 vol.% end-expiratory sevoflurane, or a continuous propofol infusion (5 to 7 $mg\,kg^{-1}\,h^{-1}$) via an infusion pump. Anaesthetics were adjusted according to the continuously measured bispectral index (BIS; Covidien, Mansfield, Massachusetts, USA) values, with the aim of keeping the BIS values in the range 40 to 60. Analgesia was maintained with a remifentanil infusion at 0.15 $\mu g\,kg^{-1}\,min^{-1}$: it was adapted to the clinical situation and discontinued 5 min before the estimated end of surgery. Piritramide (0.05 to 0.1 $mg\,kg^{-1}$) and metamizole (15 $mg\,kg^{-1}$) were administered intravenously 20 min before the end of surgery. Piritramide and metamizole are commonly used peri-operative analgesics in Germany.[18–20] Additional rescue injections of propofol were permitted for patients with undesired movements or in emergency situations.

The end of surgery was defined as time point zero (T0) for all groups and marked the onset of the emergence time measurements. According to our clinical routine, volatile agents were discontinued 5 min before the estimated end of surgery, and the fresh gas flow remained at 0.5 $l\,min^{-1}$ until the end of surgery when it was changed to 100% oxygen at 15 $l\,min^{-1}$. The propofol infusion rate was halved 5 min before the estimated end of surgery and the infusion was discontinued at the end of surgery.

Primary outcome measure

The primary objective was to analyse whether desflurane is superior to sevoflurane or propofol as regards the elapsed time from T0 to the time the patient stated his/her date of birth to command (commands were given every 20 s by a blinded investigator).

Secondary outcome measures

The elapsed times after T0 until removal of the laryngeal mask, opening the eyes, responding to a command and stating their full name to command, as well as the Recovery-Index[21] were assessed by the blinded investigator. Of note, for safety reasons, the nonblinded investigator decided when to remove the laryngeal mask.

Another secondary objective was the assessment of the frequency of upper airway complications within the three groups. Intra-operative cough and laryngospasm were assessed during the induction and maintenance of anaesthesia by the unblinded investigator. Cough and laryngospasm at emergence were assessed by the blinded investigator.

Other outcome measures

The unblinded investigator assessed the intra-operative and surgery-related data. The blinded investigator assessed the patients' pre-operative data including the baseline postoperative quality recovery scale (PQRS). In the recovery room postoperatively, the blinded investigator also assessed the patients' pain levels, postoperative nausea and vomiting, and readiness to be discharged from the recovery room; the PQRS was performed 40 min after the cessation of anaesthesia (T40) and on the first postoperative day. Recovery was scored according to the specific algorithm of the developer.[22] There were no changes to the outcome variables during the study.

Sample size

Our sample size calculations for both hypotheses (superiority of desflurane with regard to the time to state the date of birth, and noninferiority with regard to intra-operative cough) resulted in 117 (including an allowance for five drop outs) patients per group.[15] We used a type 1 error of $\alpha = 0.05$ and a power of 0.80 to calculate the sample sizes. We estimated the variances and means for the primary outcome based on the results of our previous meta-analysis.[5] The means of the time to state the date of birth were set to 5.6, 6.8 and 8.75 min for the desflurane, propofol and sevoflurane group, respectively. A common SD of 3 min was used. A sample size of 19 patients per group was required to detect a group difference. Regarding the sample size for noninferiority, a proportion between 0.07 and 0.10 was assumed in the population for the outcome intra-operative cough. A sample size between 81 and 112 patients was required to claim noninferiority (noninferiority bound of 0.20). Additional details are shown in Supplemental Digital Content 1, http://links.lww.com/EJA/A159.

Statistical analyses

Statistical analyses were performed on an intention-to-treat basis. Descriptive analyses were conducted by treatment groups using appropriate summary statistics for discrete and continuous data. The primary outcome was analysed by two-way analysis of variance, using main effects as intervention group and study site as independent variables. Dunnett's test was used for the post hoc comparison. Intra-operative cough was analysed using the Cochran–Mantel–Haenszel test, stratified by study site. Because the proportion of cough was relatively low, Newcombe confidence intervals (CIs) for distinctions in cough occurrence, stratified by study site, were calculated.[23] Inference for noninferiority was based on the upper confidence bound for the difference in proportion of cough. No additional adjustments for multiple comparisons were performed. Data for the time to state the date of birth and intra-operative cough were missing for nine and eight patients, respectively. Analyses were performed excluding these patients. Our analyses provide unbiased estimates according to the missing at random assumption.[24]

Results

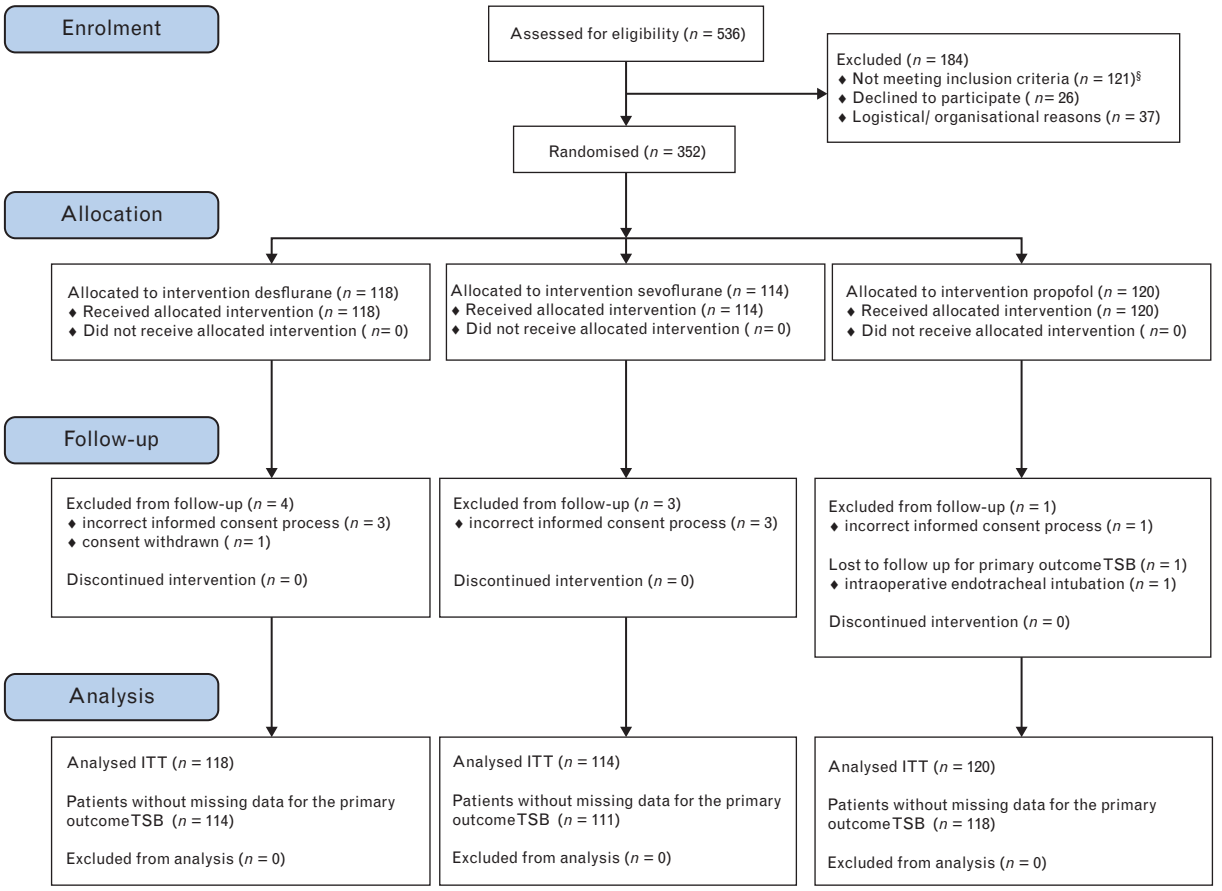
Three hundred and fifty-two patients were enrolled between February and October 2015 and randomised

into three groups: desflurane (n=118), sevoflurane (n=114) and propofol (n=120) (Fig. 1). Seven randomised patients were excluded because of a violation during the informed consent process. One randomised patient withdrew his consent in the operating room. One additional patient received intra-operative conversion of the LMA to an endotracheal airway, and the investigator failed to collect the emergence data. All patients received the allocated intervention. The trial was terminated after achievement of the planned sample size. The inclusion of one additional patient, which led to a total of 352 enrolled patients, was due to organisational reasons. The last two patients were unintentionally included in parallel in two different centres at the same time point. Patient baseline characteristics and medical histories were similar among all three groups (Table 1). However, there was a trend towards more active smokers in the desflurane group. Intra-operative anaesthesia and surgery duration as well as opioid administration were similar among the groups (Table 2). The mean anaesthetic dosage was 4.2 vol.% desflurane, 1.2 vol.% sevoflurane and 83.5 $\mu g\,kg^{-1}\,min^{-1}$ propofol. An Aldrete score at least 9 was achieved significantly faster in the desflurane group, yet the Recovery-Index remained similar among the groups (Table 2). The types of surgery are presented in Table, Supplemental Digital Content 2, http://links.lww.com/EJA/A159.

Emergence times

The primary outcome (time to state the date of birth) and the times to removal of the LMA, to respond to commands and to state their full name on command were significantly shorter in patients receiving desflurane than in patients receiving sevoflurane or propofol (Table 3). The time to open the eyes was shorter in the desflurane group compared with the sevoflurane group, but there was no difference in these times between desflurane and propofol. A secondary analysis of the primary outcome using a nonparametric test produced the same result.

Fig. 1



CONSORT-Flow chart. After screening of 536 patients, we recruited and randomised 352 patients into this study. §The particular reasons for exclusion of 121 patients, who did not meet the inclusion criteria, are drug abuse (n=26), nonfluency in German language (n=52), pre-operatively the feasibility of a laryngeal mask airway technique for the respective surgery was unclear (n=21), pre-operatively the duration of surgery was unclear (n=22). ITT, intention to treat analysis; TSB, time to state the date of birth.

Table 1 Baseline characteristics

	Desflurane, $n=118$[a]	Sevoflurane, $n=114$[a]	Propofol, $n=120$[a]
Male sex	66 (56)	58 (51)	65 (54)
ASA I/II/III	44/56/15 (37/47/13)	42/61/8 (37/54/7)	40/72/7 (33/60/6)
Age [years]	52 [37.5 to 63]	50 [36 to 60.5]	51 [31 to 64]
Height [cm]	172.7 ± 9.7	172.6 ± 9.2	172.4 ± 9.1
Weight [kg]	78.5 ± 13.0	79.2 ± 14.1	78.2 ± 13.6
BMI [kg m^{-2}]	26.3 ± 3.7	26.5 ± 3.7	26.2 ± 3.6
Nonsmoker/ex-smoker/current smoker	62 (53)/16 (14)/37 (31)	62 (54)/15 (13)/34 (30)	79 (66)/13 (11)/26 (22)
Pack years	18.9 ± 12.0	17.8 ± 19.7	16.1 ± 16.0
No pre-existing disease	46 (39)	49 (43)	56 (47)
Arterial hypertension	33 (28)	29 (25)	36 (30)
Pulmonary disease	3 (3)	1 (1)	1 (1)
Diabetes	11 (9)	9 (8)	8 (7)
Renal disease	3 (3)	1 (1)	1 (1)
Cerebrovascular disease	1 (1)	0	0
Malignant disease	11 (9)	10 (9)	5 (4)

Data are mean ± SD, median [IQR], or *n* (%). IQR, interquartile range; *n*, number of patients. [a]Missing data for desflurane ($n=3$), sevoflurane ($n=3$), propofol ($n=1$) patients.

Airway reactions

There were no differences among the anaesthetics in the occurrence of intra-operative cough ($P=0.26$), intra-operative laryngospasm ($P=0.62$), cough during emergence ($P=0.38$) or laryngospasm during emergence ($P=0.08$), and the upper limit of the CI for differences in proportions did not exceed 0.1 (Table 4). The severity of coughs was similar among the groups, and multiple coughs with an oxygen desaturation less than 95% did not occur in any patient.

Postoperative quality recovery scale

All patients showed a similar recovery in all PQRS domains, both directly after the surgery and on the first postoperative day (refer to Table, Supplemental Digital Content 3, http://links.lww.com/EJA/A159).

Other analyses

The following additional intra-operative and postoperative analyses are shown in Table, Supplemental Digital Content 4, http://links.lww.com/EJA/A159. The patients' intra-operative vital parameters and ventilation data were similar among the groups. The mean BIS values were 42.2 ± 13.6 (desflurane), 46.0 ± 14.1 (sevoflurane) and 43.4 ± 14.8 (propofol). The use of first and second-generation LMAs were equally distributed across the groups and did not influence the outcomes (adjusted analysis). Unexpected local anaesthetic infiltration occurred in four patients in the desflurane group and three in the propofol group, which was unlikely to affect the results according to our sensitivity analysis. Within 5 min after LMA removal, an Aldrete Score of at least 9 was reached in more patients in the desflurane group than in the other two groups. A Poisson test confirmed the similarity of the adverse event rate among the groups. An additional analysis adjusted for smoking status did not influence the emergence and airway reaction results.

Discussion

In patients receiving a remifentanil infusion and with an LMA in place, desflurane anaesthesia enabled significantly faster emergence with a similar frequency of upper airway complications when compared with sevoflurane or propofol. Unlike several previous studies,[5] we also included ASA III patients and the type of surgery was unrestricted, thus allowing more generalisability of the results. Moreover, to elicit more encompassing results, our study was performed during routine clinical practice in four different hospitals. In addition, our results revealed a considerably reduced occurrence of total airway complications compared with the results of the studies in our meta-analysis.[5] The total proportion of intra-operative cough and cough at emergence was previously reported to be approximately 12%,[5] which is higher than the rates of 2 and 0.3%, respectively, observed in the current study. One reason for this difference might be our predefined and nevertheless pragmatic study protocol,[15] which might also be useful for other institutions.

Study performance

Opioids have an important influence on upper airway events,[25–27] the requirements for propofol or volatile anaesthetics,[28] purposeful intra-operative movements[29] and, depending on the administration time point, also on emergence times.[30] In contrast to similar studies,[5,13,14,31] we used remifentanil during maintenance of anaesthesia, based on its predictable pharmacokinetics, excellent controllability, and liver and renal independent elimination. To date, most studies[10,32–37] have used fentanyl, typically at unstandardised dosages.

We used 20 mg lidocaine (about 0.25 mg kg^{-1}) to prevent propofol-induced pain at induction.[17] Previous studies revealed that at least double this lidocaine dose is required to suppress opioid-induced cough[38] or 1.5 to

Table 2 Intra-operative and recovery data

	Desflurane, n=118[a]	Sevoflurane, n=114[a]	Propofol, n=120[a]	Sevoflurane vs. desflurane	Propofol vs. desflurane
Duration of anaesthesia (min)	60.0 ± 34.4; 50 [33.0 to 79.0]	53.7 ± 28.4; 46 [32.5 to 64.5]	57.8 ± 28.6; 51 [35.3 to 72.8]	−6.1 (−14.1 to 1.8)	−0.8 (−8.7 to 7.0)
Surgery duration (min)	45.7 ± 32.5; 35 [23.0 to 58.8]	40.1 ± 25.8; 33 [23.0 to 49.0]	39.6 ± 27.7; 33 [20.0 to 55.0]	−5.6 (−13.1 to 1.8)	−5.2 (−12.6 to 2.2)
Anaesthetic dose (vol.% end-expiratory for desflurane and sevoflurane or $\mu g\,kg^{-1}\,min^{-1}$ for propofol	4.2 + 1.4; 4.4 [3.8 to 5.0]	1.2 ± 0.5; 1.2 [1.0 to 1.5]	83.5 ± 25.5; 83 [68.7 to 100.0]	−3.0 (−5.9 to 5.4)	N/A
Remifentanil dose [$\mu g\,kg^{-1}\,min^{-1}$]	0.15 ± 0.1; 0.15 [0.1 to 0.15]	0.15 ± 0.1; 0.15 [0.1 to 0.15]	0.15 ± 0.1; 0.15 [0.1 to 0.2]	−0.0002 (−0.006 to 0.005)	0.003 (−0.002 to 0.009)
Intra-operative piritramide [mg]	5.5 ± 2.5; 5 [3.8 to 7.5]	5.2 ± 2.6; 4.5 [3.8 to 7.5]	4.7 ± 2.4; 4.5 [3.8 to 7.4]	−0.2 (−0.7 to 0.4)	−0.6 (−1.1 to −0.0)
Time until Aldrete score ≥9 [min]	8.1 ± 10.0; 5 [4.3 to 6.0]	11.1 ± 10.1; 5 [4.6 to 19.7]	13.3 ± 16.1; 6 [4.7 to 19.4]	3.7 (1.4 to 6.3)	5.2 (2.5 to 8.2)
Recovery index	0.6 ± 0.3; 0.5 [0.4 to 0.8]	0.5 ± 0.6; 0.4 [0.3 to 0.6]	0.6 ± 0.7; 0.4 [0.3 to 0.7]	−0.10 (−0.22 to 0.01)	−0.04 (−0.16 to 0.08)

Data are mean ± SD, median [IQR], difference of means (95% CI), n (%). CI, confidence interval; IQR, interquartile range; min, minutes; n, number of patients; N/A, not applicable; surgery duration, time between skin incision and the last skin stitch, vol., volume. [a]Missing data for desflurane (n=4), sevoflurane (n=3), propofol (n=2) patients.

Table 3 Emergence variables

	Desflurane, n = 118[a]	Sevoflurane, n = 114[a]	Propofol, n = 120[a]	ANOVA[b]	Sevoflurane vs. desflurane[c]	Propofol vs. desflurane[c]
Time to state the date of birth	8.1 ± 3.6; 7.1 [6.0 to 10.0]	10.1 ± 4.0; 10.0 [7.1 to 12.5]	9.8 ± 5.1; 8.7 [6.6 to 12.6]	<0.01	1.9 (0.8 to 3.0) P < 0.01	1.5 (0.4 to 2.6) P < 0.01
Time to remove the laryngeal mask	6.9 ± 3.3; 6.1 [4.7 to 8.7]	8.7 ± 3.9; 8.9 [5.6 to 11]	8.2 ± 4.1; 7.3 [5.5 to 10]	<0.01	1.8 (0.8 to 2.7) P < 0.01	1.1 (0.2 to 2.1) P < 0.04
Time to open the eyes on command	6.8 ± 3.5; 6.0 [4.4 to 8.3]	8.6 ± 4.1; 8.8 [5.2 to 11]	8.0 ± 4.4; 7.0 [5.2 to 9.9]	<0.01	1.9 (0.9 to 2.9) P < 0.01	1.1 (0.1 to 2.1) P < 0.06
Time to respond to the command (press hand)	7.54 ± 3.6; 6.7 [5.3 to 9.0]	9.6 ± 4.1; 9.7 [6.3 to 12.3]	9.10 ± 4.9; 7.7 [5.8 to 11.3]	<0.01	2.0 (1.0 to 3.1) P < 0.01	1.4 (0.3 to 2.5) P < 0.02
Time to state the full name on command	8.0 ± 3.6; 7.1 [5.7 to 9.7]	9.9 ± 4.0; 9.8 [6.9 to 12.5]	9.70 ± 5.1; 8.6 [6.3 to 12.9]	<0.01	1.9 (0.8 to 3.0) P < 0.01	1.5 (0.4 to 2.6) P < 0.01

Data are mean ± SD, median [IQR], difference of means (95% CI). ANOVA, analysis of variance; CI, confidence interval; IQR, interquartile range; n, number of patients. [a]Missing data for desflurane (n = 4), sevoflurane (n = 3) and propofol (n = 2) patients. [b]Two-way ANOVA with independent variables intervention group and study site. [c]Based on Dunnett's test.

Table 4 Airway reactions

	Desflurane *n* (%)	Sevoflurane *n* (%)	Propofol *n* (%)	Cochran–Mantel–Haenszel group difference	Desflurane vs. sevoflurane[b]	Desflurane vs. propofol[b]
Intra-operative cough	(*n* = 118)[a]	(*n* = 114)[a]	(*n* = 120)[a]			
Yes/no	4 (3)/110 (93)	1 (1)/110 (96)	2 (2)/117 (98)	*P* = 0.26	(−4 to 9)	(−3 to 9)
Single, $SpO_2 > 95\%$/multiple, $SpO_2 > 95\%$/multiple, $SpO_2 < 95\%$	2 (2)/2 (2)/NA	0 (0)/1 (1)/NA	1 (1)/1 (1)/NA			
No data	4 (3)	3 (3)	1 (1)			
Intra-operative laryngospasm	(*n* = 118)[a]	(*n* = 114)[a]	(*n* = 120)[a]			
Yes/no	4 (3)/110 (93)	3 (3)/108 (95)	2 (2)/117 (98)	*P* = 0.62	(−6 to 7)	(−4 to 8)
Once/twice	3 (3)/1 (1)	3 (3)/0 (0)	2 (2)/0 (0)			
No data	4 (3)	3 (3)	1 (1)			
Cough at emergence	(*n* = 118)[a]	(*n* = 114)[a]	(*n* = 120)[a]			
Yes/no	1 (1)/113 (96)	0 (0)/111 (97)	0 (0)/118 (98)	*P* = 0.38	(−3 to 7)	(−3 to 7)
Single, $SpO_2 > 95\%$/multiple, $SpO_2 > 95\%$/multiple, $SpO_2 < 95\%$	1 (1)/NA/NA	0 (0)/NA/NA	0 (0)/NA/NA			
No data	4 (3)	3 (3)	2 (2)			
Laryngospasm at emergence	(*n* = 118)[a]	(*n* = 114)[a]	(*n* = 120)[a]			
Yes/no	2 (2)/112 (95)	0 (0)/111 (97)	0 (0)/119 (99)	*P* = 0.08	(−2 to 7)	(−2 to 8)
Once/twice	2 (2)/NA	0 (0)/NA	0 (0)/NA			
No data	4 (3)	3 (3)	1 (1)			

Data are mean ± SD, median [IQR], *n* (%), (95% confidence interval for the difference in proportions[b]). IQR, interquartile range; *n*, number of patients; NA, not applicable.
[a] Data missing for desflurane (*n* = 4), sevoflurane (*n* = 3) and propofol (*n* = 1) patients [b] Newcombe confidence intervals stratified by study site.

$2\,mg\,kg^{-1}$ to suppress mechanically or chemically induced cough.[39,40] The low incidence of cough during our entire study is unlikely to be attributable to the injection of lidocaine during anaesthesia induction, as lidocaine has a short effect duration of 5 to 8 min.[41]

Our study reports the mean end-expiratory volatile concentrations and not the MAC, as the latter may be imprecise, because it is affected by various variables.[42] The desired end-tidal volatile concentrations and propofol dosages originated from our clinical experience and were adapted continuously to the patients' needs during anaesthesia. Our low end-tidal anaesthetic concentrations and the low mean propofol dosage may be explained by the remifentanil dose we used.[43] As recommended by the ASA guideline, we monitored the depth of anaesthesia using clinical techniques and conventional monitoring systems.[44] We used BIS monitoring as a surrogate indicator of the hypnotic drug effect to enhance the comparability of anaesthesia depth across the groups.[43] Previous studies have shown a significant lack of homogeneity with regard to the anaesthetics used, and to the best of our knowledge, only one study utilised BIS monitoring.[5] A rapid induction with high desflurane concentrations was avoided because this may enhance the risk of increased inspiratory resistance and consequent upper airway complications.[2] Thus, we developed a detailed protocol to standardise volatile anaesthetic administration.[15] This process was easily implemented in our clinical routine and resulted in improved comparability.

In contrast to other studies,[5] we sought to minimise the bias induced by additional drugs that may affect upper airway complications and emergence times, such as midazolam, propofol for induction, metamizole and piritramide. The aforementioned medication was used according to the study protocol, and the dosage was comparable among the groups. However, we cannot exclude individual differences in the sensitivity to these drugs. In addition, waiving or administering extremely low doses of pre-operative midazolam has shown inconsistent results with regard to intra-operative cough.[5,6,33,37] We acknowledge that the residual effects of our premedication with midazolam may have negatively influenced the emergence and recovery outcomes.[45] Future studies should consider avoiding the use of midazolam.

Selection and detection bias were minimised by strict allocation concealment prior to patient recruitment as well as the use of two independent investigators for the outcome assessment. Notably, the intra-operative investigator could not be blinded because of safety reasons.

Emergence times

Our emergence results are consistent with our meta-analysis[5] and more recent studies.[14,31] In contrast to almost all previously performed studies, we used the primary outcome variable 'time to state the date of birth', which demands a higher level of consciousness than 'time to open the eyes'. Eye opening on command may be a type of unconscious reaction, likely explaining the similar results for this outcome in comparisons of desflurane and propofol and of desflurane and sevoflurane observed in a recent study.[13]

It remains unclear why our study failed to show a difference in the Recovery-Index despite a shorter emergence and faster achievement of an Aldrete score at least 9 with desflurane.

Different pharmacokinetics of volatile anaesthetics and propofol are a challenge for comparability in clinical trials.

Target controlled infusion systems and closed-loop controllers were not available in our institutions. Our decision to halve the propofol infusion 5 min before the estimated end of surgery, while turning off both inhaled anaesthetics under the unchanged low fresh gas flow of 0.5 to 1 l min^{-1}, originated from our clinical experience and was performed to increase comparability. Turning off the vapouriser without increasing the fresh gas flow is known to maintain adequate alveolar drug concentrations with a slow change of the end-expiratory concentration.[46] This was assumed to be equivalent to the propofol handling. However, in clinical practice, practitioners probably deviate from this approach.

The benefit of a 2-min faster emergence after desflurane anaesthesia is debatable. It would only have a clinical relevance if it is associated with differences in patient outcomes or resource utilisation. However, the PQRS, which displays the patient outcome, was similar across the three groups. Yet, the reduced variability in emergence times, especially when compared with propofol, may be a more important finding. Propofol had the largest range of emergence times, thus reducing its predictability. Further, it might be of clinical significance that at 5 min after removal of LMA, the Aldrete Score of at least 9 was achieved in about 20 patients more in the desflurane group compared with the other two groups. This may support an earlier discharge from the recovery room.

Airway reactions

A recent study reported significantly more peri-operative coughs (including both intra-operative cough and cough at emergence) in the desflurane group (35%) than in the sevoflurane group (12%).[14] The uncombined single outcomes were not different. Notably, this study[14] also used volatile anaesthetics before LMA insertion, and patients in the desflurane group received less fentanyl. The large difference in the proportion of coughs compared with our low rate of coughs might also be explained by the difference in the administration of anaesthesia.

In the current study, the similar frequency of airway complications within the three groups may reduce prejudices against desflurane in patients with an LMA. However, we acknowledge that our study was powered only for the detection of differences in the occurrence of intra-operative cough.

The presence of only two laryngospasms at emergence in the desflurane group should be interpreted with caution owing to the low event rate and lack of statistical power. All airway events were handled properly and did not entail serious consequences.

Postoperative quality recovery scale

Postoperative recovery was similar, including physiological, cognitive and functional recovery. In particular, cognitive recovery has yielded contrary results in previous studies. Although two studies demonstrated an improved recovery with desflurane compared with sevoflurane,[11,47] another study revealed a slight disadvantage,[13] and a further study showed no difference.[14] Notably, approximately two-thirds of all our patients had not recovered on the first postoperative day with respect to all five analysed domains compared with the baseline assessment.

Limitations

There were several limitations to our study. First, we could not exclude an effect of remifentanil or piritramide on our outcomes. Therefore, our results must be considered in association with the use of remifentanil and piritramide. It remains unclear whether the administration of different opioids would have led to the same results.

Second, equivalent BIS values cannot be assumed to reflect equivalent brain states when different general anaesthetic agents are used. Therefore, we cannot conclude that anaesthetic exposure was equipotent in the three groups. However, BIS is one of the most widely used brain electrical activity monitors in clinical practice,[43,44] and we did our best to achieve relatively equipotent anaesthesia depth in this study, which was performed during routine clinical practice. However, patients vary and an array of individual variables may influence the effects of anaesthetics on the depth of anaesthesia. If higher concentrations of sevoflurane, desflurane or propofol had been used, the incidence of complications might have been different, and our approach to the termination of anaesthesia at the end of surgery might have influenced our results.

Third, the use of a LMA can create a risk of performance bias because of operator-dependent differences during LMA insertion: misplaced LMAs could influence airway reactions.[48]

In addition, our results must be considered in connection with our dedicated study protocol. Deviations from the protocol may lead to different results, particularly with regard to the low incidence of upper airway complications we observed compared with that previously reported. Finally, this study was powered only for the time to state the date of birth, and intra-operative cough; all other outcomes must be interpreted with caution.

Conclusion

In this large multicentre trial with its low bias, we established that, in the presence of a continuous infusion of remifentanil, desflurane is superior in terms of faster emergence and is similar in terms of intra-operative cough to sevoflurane or propofol. The clinical relevance of the faster emergence after desflurane compared with sevoflurane or propofol remains debatable. Our total incidence of airway complications was lower as described

in literature and may be due to our applied standardised anaesthesia protocol.

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