EJA

Eur J Anaesthesiol 2015; **32:**106–116

OPEN

ORIGINAL ARTICLE

Airway reactions and emergence times in general laryngeal mask airway anaesthesia

A meta-analysis

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BACKGROUND Desflurane's short emergence time supports fast track anaesthesia. Data on the rate of upper airway complications and emergence time when desflurane is used with laryngeal mask airway (LMA) are controversial and limited.

OBJECTIVES To compare recovery time variables and the rates of upper airway adverse events in patients with an LMA undergoing general surgery with desflurane, sevoflurane, isoflurane or propofol anaesthesia.

DESIGN A systematic review and meta-analysis of randomised controlled trials (RCTs).

DATA SOURCES A systematic search for eligible RCTs in Embase (Elsevier) and in PubMed (National Library of Medicine) databases up to September 2013.

ELIGIBILITY CRITERIA RCTs investigating the rates of cough overall, cough at emergence, laryngospasm, time to eye opening, time to removal of the LMA, time to respond to command and time to state date of birth in patients with an LMA, during emergence from desflurane, sevoflurane, isoflurane or propofol anaesthesia.

RESULTS Thirteen RCTs were included and analysed. We found a strong interstudy variability. There was no difference in the rates of upper airway events between desflurane and sevoflurane or between desflurane and a control group consisting of all the other anaesthetics combined. Comparing desflurane (n = 284) with all other anaesthetic groups ($n = 313$), the risk ratio [95% confidence interval (95% CI)] was 1.12 (0.63 to 2.02, $P = 0.70$). Cough at emergence was only measured in patients receiving desflurane ($n = 148$) and sevoflurane ($n = 146$): the risk ratio (95% CI) was 1.49 (0.55 to 4.02, $P = 0.43$). Laryngospasm was rare and there was no significant difference in its incidence when desflurane (n = 262) was compared with all other anaesthetics combined ($n = 289$; risk ratio 1.03; 95% CI 0.33 to 3.20, $P = 0.96$). The times of all emergence variables were significantly faster in the desflurane group than in all other groups.

CONCLUSION When using an LMA, upper airway adverse reactions in association with desflurane anaesthesia were no different from those noted with sevoflurane, isoflurane or propofol anaesthesia. Emergence from general anaesthesia with desflurane is significantly faster than all the other anaesthetics. Due to interstudy variations and the small size of the trials, further large-scale, multicentre studies are required to confirm or refute the results of this meta-analysis.

Published online 11 November 2014

This article is accompanied by the following Invited Commentary:

Afshari A, Wetterslev J. When may systematic reviews and meta-analyses be considered reliable? *Eur J Anaesthesiol* 2015; **32**:85–87.

Introduction

Background

The low blood gas solubility coefficient of desflurane supports fast track general anaesthesia, even in obese patients.[1] In comparison to an endotracheal tube (ETT), a laryngeal mask airway (LMA) reduces postoperative airway-connected complications during general

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 DOI:10.1097/EJA.0000000000000183

anaesthesia.[2] However, desflurane has airway irritant properties, and there is controversy as to whether these are worse than or similar to those of other volatile anaesthetics (sevoflurane, isoflurane) or to a propofol-based anaesthetic.[1] Trials comparing the risk of intraoperative upper airway complications (e.g. coughing, laryngospasm) between desflurane and other common anaesthetics are limited. Recently, de Oliveira *et al.*[3] published a meta-analysis comparing upper airway adverse events, and concluded that there was a lack of evidence that desflurane caused a greater incidence of upper airway adverse events than sevoflurane. In that meta-analysis,[3] there were no data regarding recovery times.

Objectives

We compared desflurane with other commonly used anaesthetics in this meta-analysis of randomised controlled clinical trial (RCT) data from patients undergoing general anaesthesia with the aid of an LMA. Our primary endpoints were the rate of upper airway complications: cough overall; cough at emergence and laryngospasm total. Secondary endpoints were related to the speed of emergence from anaesthesia: time to open eyes (TOE); time to respond to command (TRC); time to remove LMA (TLR); and time to state date of birth (TSB).

Materials and methods

Protocol

Before commencing this meta-analysis, all authors agreed the inclusion and exclusion criteria. The manuscript was prepared in accordance with the PRISMA guidelines.[4] The protocol was not published.

Eligibility criteria

We included only RCTs with patients at least 18 years of age undergoing general anaesthesia with an LMA following an intravenous induction. These trials compared desflurane-maintained anaesthesia with anaesthesia maintained by propofol, or sevoflurane or isoflurane. These RCTs had to present data for at least one of our prespecified outcome variables: cough overall, cough at emergence, laryngospasm total, TOE, TRC, TLR and TSB. Publications in all languages were included in the search. Non-English publications were translated into English (TransPerfect Translations International, Chicago, USA).

Systematic search

The following databases were used to identify potential RCTs: PubMed (National Library of Medicine, 1946 to September 2013) and Embase (Elsevier, 1947 to September 2013). The search words used were a combination of desflurane, sevoflurane, isoflurane, propofol, laryngeal masks. Full details of the search criteria can be obtained from the authors.

The references listed in those studies meeting the screening criteria were searched for further relevant RCTs.

Study selection and data collection

In the first step, the two investigators (M.C., A.S.) screened the titles independently and removed studies that did not meet the prespecified screening criteria, or were duplicate studies. According to a predefined data extraction sheet, the remaining articles were screened on the basis of the abstract. Potentially eligible trials were analysed in detail on the basis of their full text. Disagreements were discussed between the two primary investigators. In the event of persistent disagreement, an additional author would be involved in the discussion until consensus was achieved. One Spanish trial was translated into English before the inclusion.[5] One author was contacted to provide us with their results regarding the variables TOE and TRC in mean and standard deviation values.[6] The formula developed by Hozo *et al.*[7] was used to calculate the mean and standard deviations for TOE in one publication.[8]

Table 1 Anaesthetic agents and outcomes of the included trials

	Ashworth and Smith [16]	De Oliveira Jr *et al.*[6]	Dolk *et al.*[14]	Eshima *et al.*[11]	Gupta *et al.*[15]	Lema *et al.*[5]	Mahmoud *et al.*[8]	McKay *et al.*[10]	McKay *et al.*[17]	McKay *et al.*[18]	Naidu-Sjösvärd *et al.*[19]	Saros *et al.*[13]	White *et al.*[9]
Anaesthetic agent													
Des [*n*]	30	40	34	63	25	43	31	31	55	60	25	35	65
Sev [*n*]	–	40	34	64	–	41	29	33	55	60	25	35	65
Iso [*n*]	30	–	–	–	25	–	–	–	–	–	–	–	–
Prop [*n*]	30	–	34	–	–	–	–	–	–	–	–	–	–
Outcome studied													
CO	Yes	Yes	–	Yes	–	–	Yes	–	Yes	–	–	–	Yes
CE	–	Yes	–	–	–	Yes	–	–	–	–	–	–	Yes
LS	Yes	Yes	–	Yes	–	Yes	Yes	–	Yes	–	–	–	–
TOE	Yes	–	–	–	Yes	–	Yes	–	–	–	Yes	–	Yes
TLR	Yes	–	Yes	–	Yes	–	–	–	–	–	–	Yes	–
TRC	Yes	–	–	Yes	–	–	–	Yes	Yes	Yes	–	Yes	Yes
TSB	Yes	–	Yes	–	Yes	–	–	–	–	–	Yes	–	–

CE, cough at emergence; CO, cough overall; Des, desflurane; Iso, isoflurane; LS, laryngospasm; Prop, propofol; Sev, sevoflurane; TLR, time to remove LMA; TOE, time to open eyes; TRC, time to respond to command; TSB, time to state the date of birth; Yes, outcome studied; – outcome not studied.

Data extraction

We extracted the data summarised in Table 1[9–11,13–18] and in the supplemental digital content (SDC, http://links.lww.com/EJA/A58) 1 to 8 from the identified publications. Only values of our prespecified primary and secondary endpoints, presented either as counts of events, or as means and standard deviation, were used for our analysis.

Assessment of risk of bias

Using the Cochrane Collaboration's tool for assessing risk of bias (http://handbook.cochrane.org/chapter_8/table_8_5_a_the_cochrane_collaborations_tool_for_assessing.htm), two authors (M.C., A.S.) evaluated each trial independently (see SDC 8, http://links.lww.com/EJA/A58).

Statistics

These meta-analyses were performed with RevMan 5.2. We considered a clinical and methodological heterogeneity of the included trials and therefore a random-effects model was used. The percentage of interstudy variation was acquired by I^2. Values more than 50% were considered as moderately heterogeneous. Risk ratio and 95% confidence intervals (95% CIs) were calculated for the occurrence of the dichotomous outcome variables cough overall, cough at emergence and laryngospasm total; the continuous outcomes (TOE, TRC, TLR, TSB) were calculated by weighted mean differences (WMDs) of the mean values and standard deviations in minutes. P values less than 0.05 were assumed as statistically significant. We performed subgroup analyses of trials by comparing desflurane to sevoflurane only. If at least 10 trials were identified, then to determine publication bias we planned to create funnel plots and to use Egger's test.

Results

Our primary search strategy identified 2090 publications. Only 14 trials met our inclusion criteria, reporting at least on one of our endpoint variables.[5,6,8–19] One trial, comparing desflurane with sevoflurane, investigating the rate of coughs, was excluded, as the number of coughs was not accessible from the data.[12] We could not include the data (TOE and TRC) of De Oliveira *et al.*[6] in our analysis, as we did not receive an answer regarding their mean and standard deviation values. The flowchart (Fig. 1) illustrates the search and exclusion strategy, leaving 13 RCTs for analysis.[5,6,8–11,13–19] An overview of the selected trials, the anaesthetic agents used and measured outcome variables is summarised in Table 1.

Participants

In total, 1143 patients were included in the 13 trials. The number of patients per group did not differ significantly (Table 1). The patient characteristics are shown in SDC 1, http://links.lww.com/EJA/A58 and discussed in detail in the SDC 2, http://links.lww.com/EJA/A58. Patient baseline characteristics showed a high interstudy variability.

Study protocols

The protocols of the trials showed many differences that led to considerable heterogeneity. Examples are the use/nonuse of midazolam, lidocaine, opioids, nitrous oxide, local and regional anaesthesia, as well as different ventilation modes and anaesthetic concentrations (SDC 3 to 7, http://links.lww.com/EJA/A58).

It is important to note that the primary endpoint in some trials was not one of our primary endpoints, and so those trials were not powered to detect significant differences for our variables. The primary endpoints on which the studies were powered are summarised in Table 2.

Risk of bias

The results of the risk of bias assessment are summarised in Table 3. Only two trials described the random sequence generation and the allocation concealment.[5,6] Three trials reported the random sequence generation, but failed to report the allocation concealment.[9,11,17] There was a high risk of performance bias regarding the blinding of patients and personnel in all the trials. Detection bias showed a high risk in four trials, as the outcome assessor was not blinded.[13–15,19] In one trial, only the assessment of the intraoperative events (e.g. cough overall) was not blinded and consequently there was a high risk of detection bias for respiratory complications.[16] There was a low risk of attrition bias across all trials with complete reporting of outcome data and losses to follow-up. The selective reporting bias was unclear in all trials, as we did not assess the original study protocol.

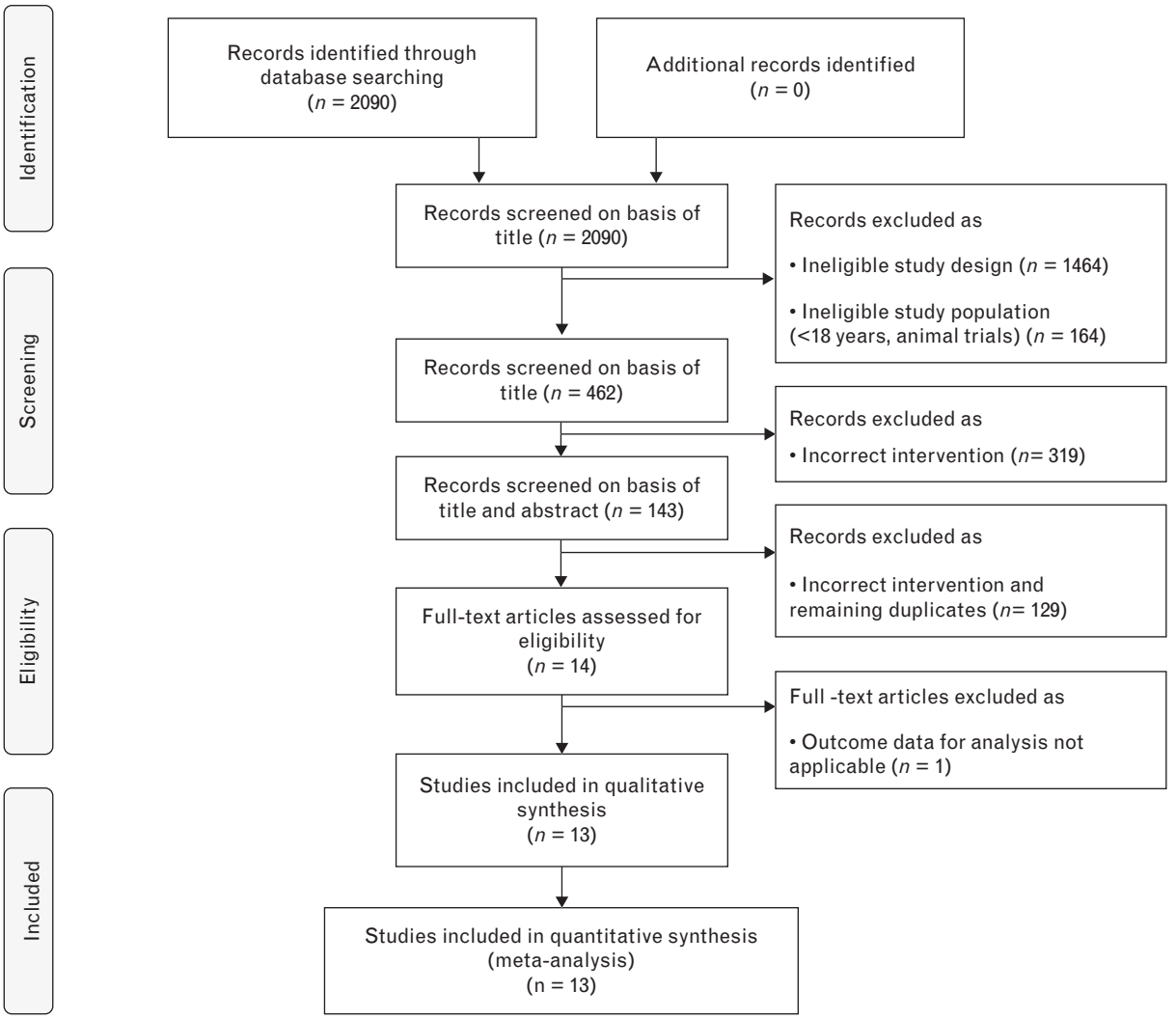
The following factors are particularly important for interpretation of the study results. The concentration of the anaesthetics was not controlled in the trials. The administration of midazolam and opioids at induction, and the repeat administration of opioids during anaesthesia were not strictly predefined in five protocols.[5,10,11,17,18] With respect to other potential biases, we noted a high risk in three trials.[10,11,17] In two of these, it was not known who received midazolam and fentanyl at induction.[11,17] McKay *et al.*[17] included only smokers, and the groups differed significantly with regard to smoking: the patients in the desflurane group had been exposed to significantly more pack years than the sevoflurane group. In the third trial, significantly more patients in the sevoflurane group received regional anaesthesia and orthopaedic surgery than in the desflurane group.[10]

Effects of interventions primary outcomes: upper airway complications

Cough overall

Occurrence of cough at anaesthesia induction, during surgery and during the recovery phase was subsumed under cough overall.[6,8,9,11,16,17] There was no significant difference in cough overall between desflurane ($n = 284$) and the control group ($n = 313$) consisting of propofol, sevoflurane and isoflurane anaesthetics combined [risk

Fig. 1



Flowchart. PRISMA flow diagram showing literature results.

ratio (95% CI) 1.12 (0.63 to 2.02), $P = 0.70$]. The heterogeneity with $I^2 = 31$ was low to moderate, as previously described by Higgins *et al.*[20] (Fig. 2a). In a subgroup analysis of trials comparing only desflurane ($n = 254$) with sevoflurane ($n = 253$), we found a similar effect [risk ratio (95% CI) 1.12 (0.56 to 2.22), $P = 0.75$] and a moderate heterogeneity with $I^2 = 44\%$ (Fig. 2a).

Table 2 Original primary endpoints of the included trials

Trial	Originally described primary endpoint
Ashworth and Smith [16]	Not known
De Oliveira Jr *et al.*[6]	Eye opening
Dolk *et al.*[14]	Time to state the name and birth
Eshima *et al.*[11]	Airway irritation
Gupta *et al.*[15]	Postoperative recovery
Lema *et al.*[5]	Event rate of cough
Mahmoud *et al.*[8]	Efficacy of the anaesthetics
McKay *et al.*[10]	Recovery of airway reflexes
McKay *et al.*[17]	Airway responses in smokers
McKay *et al.*[18]	Time to respond to command in obese patients
Naidu-Sjösvärd *et al.*[19]	Recovery characteristics
Saros *et al.*[13]	Emergence time
White *et al.*[9]	Resuming normal activities on the first postoperative day

In a further nonprespecified subgroup analysis of cough overall, we excluded the trial of Ashworth and Smith[16] because of high risk of detect9ion bias. The remaining trials, with a low risk of detection bias, compared only desflurane and sevoflurane. The analysis of these studies with a low risk detection bias produced the same results to those of the prespecified subgroup analysis of desflurane vs. sevoflurane (Fig. 2a).

Cough at emergence

Three clinical trials assessed cough in the recovery phase.[5,6,9] They compared only desflurane ($n = 148$) and sevoflurane ($n = 146$). There was no statistically significant

Table 3 Risk of bias

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of patients and personnel (performance bias)	Blinding of outcome assessment (detection bias) respiratory complications	Blinding of outcome assessment (detection bias) recovery parameters	Incomplete outcome data (attrition bias)	Selective reporting (Reporting bias)	Other bias
Ashworth and Smith [16]	?	?	+	+	−	−	?	−
De Oliveira Jr *et al.*[6]	−	−	+	−	−	−	?	−
Dolk *et al.*[14]	?	?	+	N.A.	+	−	?	−
Eshima *et al.*[11]	−	?	+	−	−	−	?	+
Gupta *et al.*[15]	?	?	+	N.A.	+	−	?	−
Lema *et al.*[5]	−	−	+	−	N.A.	−	?	−
Mahmoud *et al.*[8]	?	−	+	N.A.	−	−	?	−
McKay *et al.*[10]	?	?	+	−	−	−	?	+
McKay *et al.*[17]	−	?	+	−	−	−	?	+
McKay *et al.*[18]	?	?	+	N.A.	−	−	?	−
Naidu-Sjösvärd *et al.*[19]	?	?	+	N.A.	+	−	?	−
Saros *et al.*[13]	?	−	+	+	+	−	?	−
White *et al.*[9]	−	?	+	−	−	−	?	−

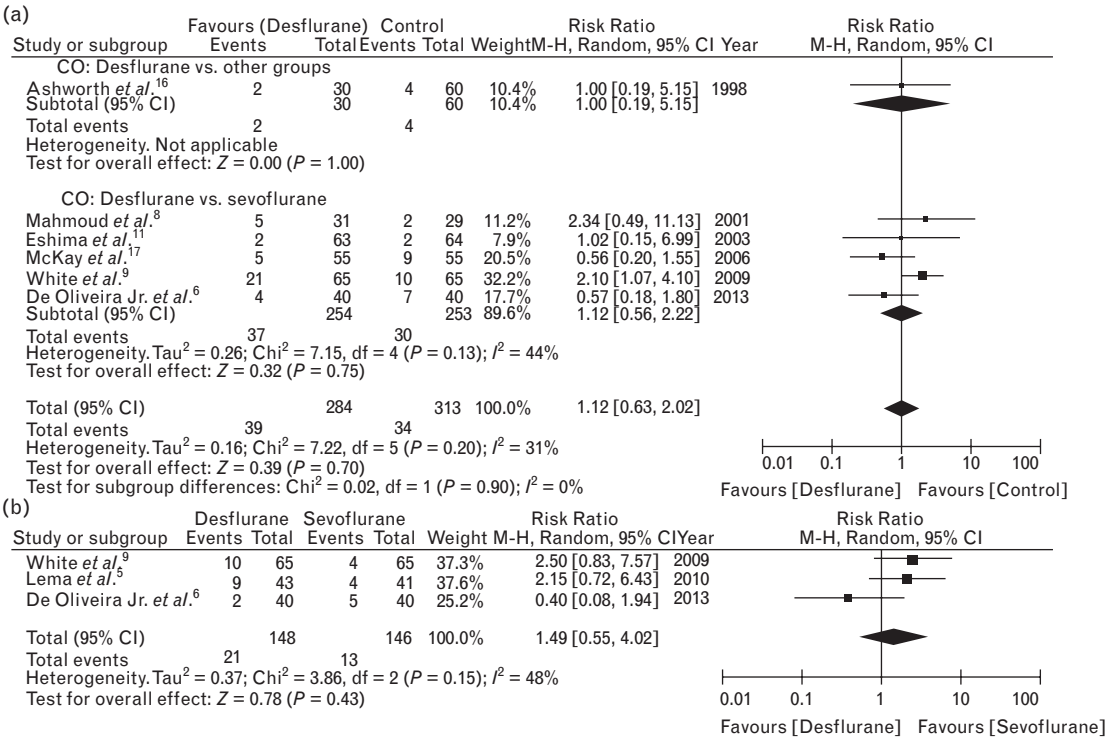
N.A., not applicable. +, high risk; −, low risk; ?, risk not known.

difference [risk ratio (95% CI) 1.49 (0.55 to 4.02), $P = 0.43$], with a moderate heterogeneity $I^2 = 48\%$ (Fig. 2b).

Laryngospasm

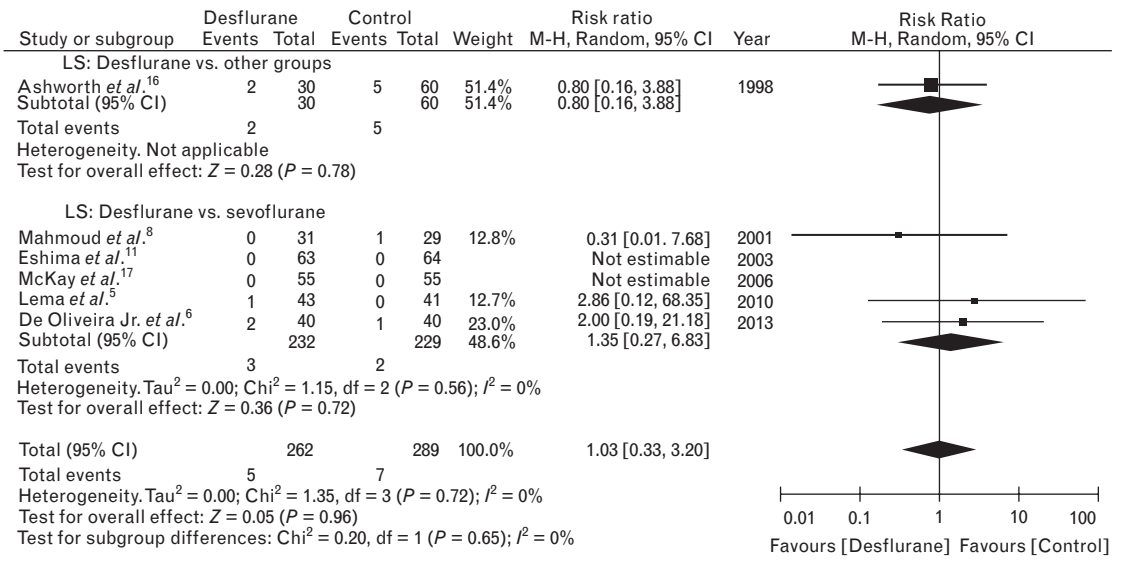
There was no significant difference in the occurrence of laryngospasm in the six trials reporting this variable. The risk ratio (95% CI) was 1.03 (0.33 to 3.20; $P = 0.96$) when the combined anaesthetics (propofol, sevoflurane, isoflurane) ($n = 289$) were compared with desflurane ($n = 262$) (Fig. 3).[5,6,8,11,16,17] In two of these trials, no laryngospasm was noted.[11,17] None of the cases of laryngospasm had any untoward outcome. The heterogeneity was low with

Fig. 2



Occurrence of cough overall (CO) and cough at emergence (CE). (a) CO: Summary risk ratios (RR) for each subgroup shown as subtotals. Summary risk ratios (RR) for desflurane vs. all other agents shown as total. RR for individual studies = square on Forrest plot, with 95% CI of difference, solid line. Diamonds, pooled estimate and uncertainty for the combined effect. (b) CE: Summary risk ratios (RR) calculated with random effects method. RR for individual studies, square on Forrest plot, with 95% CI of difference, solid line. Diamonds, pooled estimate and uncertainty for the combined effect.

Fig. 3



The occurrence of laryngospasm: desflurane vs. other groups and desflurane vs. sevoflurane. Summary risk ratios (RR) calculated with random effects method for each subgroup shown as subtotals. Summary risk ratios (RR) calculated with random effects method for desflurane vs. all other agents shown as total. RR for individual studies, square on Forrest plot, with 95% CI of difference, solid line. Larger sized square and thicker 95% CI line, larger sample size. Diamonds, pooled estimate and uncertainty for the combined effect.

$I^2 = 0$. The subgroup analysis for laryngospasm total when desflurane ($n = 232$) as compared with sevoflurane ($n = 229$) showed a similar result [risk ratio (95% CI) 1.35 (0.27 to 6.83, $P = 0.72$)] (Fig. 3).[5,6,8,11,17]

Secondary outcomes: recovery times

Time to open eyes

In the overall analysis of all anaesthetic agents (propofol, sevoflurane, isoflurane) ($n = 204$) vs. desflurane ($n = 176$), we found a significantly shorter TOE in the desflurane group [WMD (95% CI) of −2.60 (-4.02 to −1.17) min $P < 0.001$][8,9,15,16,19] with high heterogeneity, $I^2 = 87\%$ (Fig. 4a). The subgroup analysis of desflurane ($n = 121$) vs. sevoflurane ($n = 119$) showed a similar effect [WMD (95% CI) of 3.8 (4.6 to 3.0) min ($P < 0.001$)], with minimal heterogeneity (Fig. 4a).[8,9,19]

Time to remove laryngeal mask airway

The time to removal of the LMA was shorter in the desflurane group ($n = 124$) than all other anaesthetics combined (propofol, sevoflurane, isoflurane) ($n = 188$), WMD (95% CI) −1.11 (−1.71 to −0.52) min ($P < 0.01$).[13–16] Heterogeneity was moderate with $I^2 = 63\%$ (Fig. 4b). Analysing only trials that compared desflurane with sevoflurane produced a similar result, with low heterogeneity (Fig. 4b).[13,14]

Time to respond to command

We found a significantly shorter TRC in the desflurane group ($n = 339$) vs. all other agents combined (propofol, sevoflurane, isoflurane) ($n = 372$), WMD (95% CI) −1.84 (−2.38 to −1.31) min ($P < 0.001$), with a low heterogeneity ($I^2 = 40\%$) (Fig. 5a).[9–11,13,16–18] The subgroup analysis of desflurane vs. sevoflurane revealed the same outcome ($P < 0.001$) (Fig. 5a).[9–11,13,17,18]

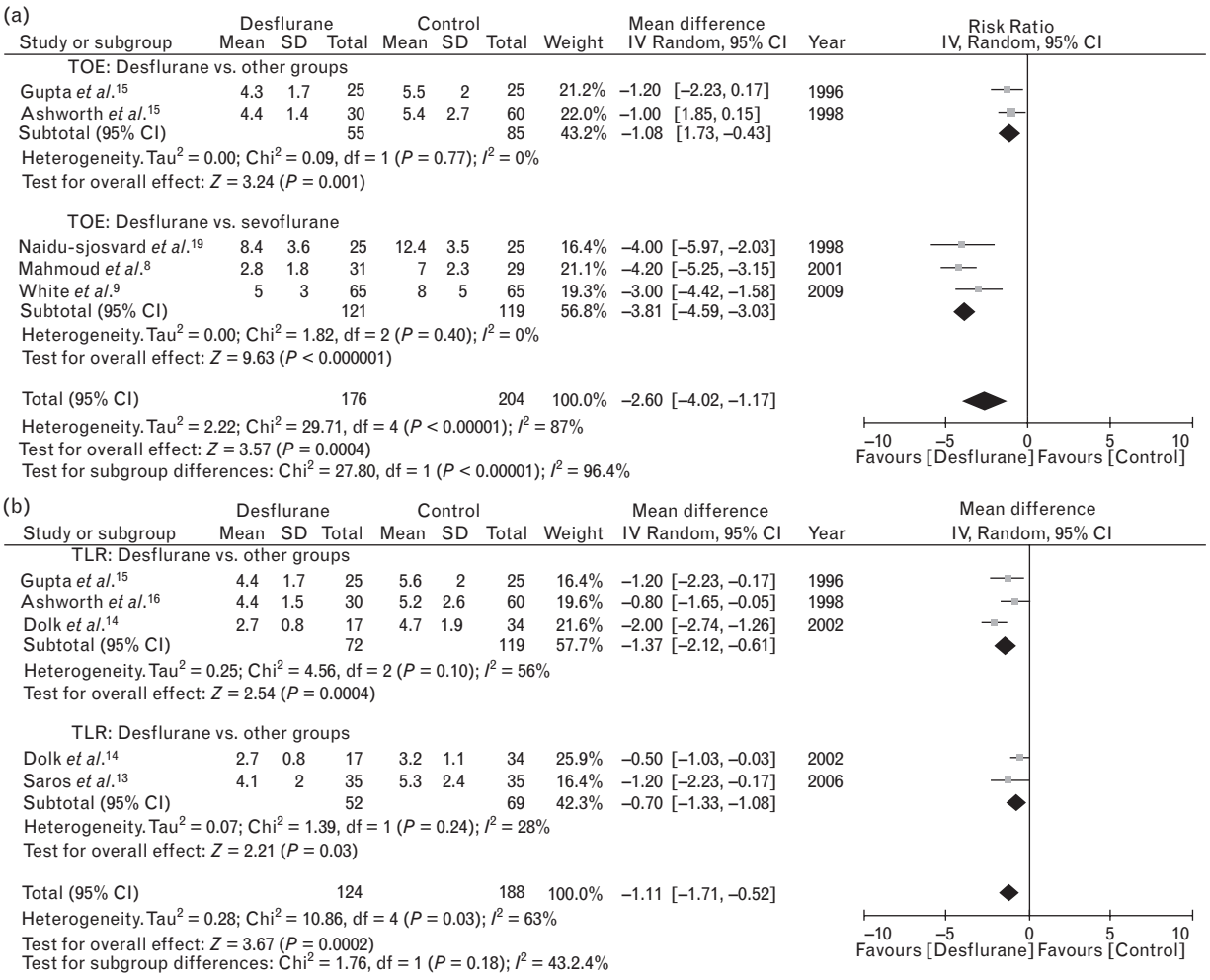
Time to state the date of birth

Four studies determined the time from discontinuing the anaesthetic agent until that patient was able to state their date of birth.[14–16,19] With a high heterogeneity ($I^2 = 86\%$), TSB was much faster in the desflurane group ($n = 114$) than all other anaesthetic agents combined (propofol, sevoflurane, isoflurane) ($n = 178$), WMD (95% CI) −1.92 (−3.09 to −0.75) min ($P < 0.001$) (Fig. 5b). When desflurane ($n = 42$) was compared with sevoflurane ($n = 59$) TSB shorter, WMD (95% CI) −2.5 (−6.7 to 1.7) min, this was not statistically significant: $P = 0.24$ (Fig. 5b).[14,19] Heterogeneity was high: $I^2 = 93$.

Discussion

There are only a few RCTs comparing desflurane with other commonly used anaesthetics (sevoflurane, propofol, isoflurane) in patients undergoing general anaesthesia with an LMA. We were unable to identify a significant difference in the occurrence of upper airway adverse events (cough overall, cough at emergence and laryngospasm total) between desflurane and the other three anaesthetics. For the outcome variable cough at emergence, only trials comparing desflurane with sevoflurane were available for analysis. With regard to cough overall and laryngospasm total, our results are the same as those of the recently published meta-analysis by De Oliveira

Fig. 4



Forrest plot time to open eyes (TOE) and time to remove LMA (TLR). Summary mean difference calculated with random effects method for each subgroup shown as subtotals. Summary mean difference calculated with random effects method for desflurane vs. all other agents shown as total. Mean difference for individual studies, square on Forrest plot, with 95% CI of difference, solid line. Diamonds, pooled estimate and uncertainty for the combined effect. Time is represented in minutes. (a) TOE. (b) TLR.

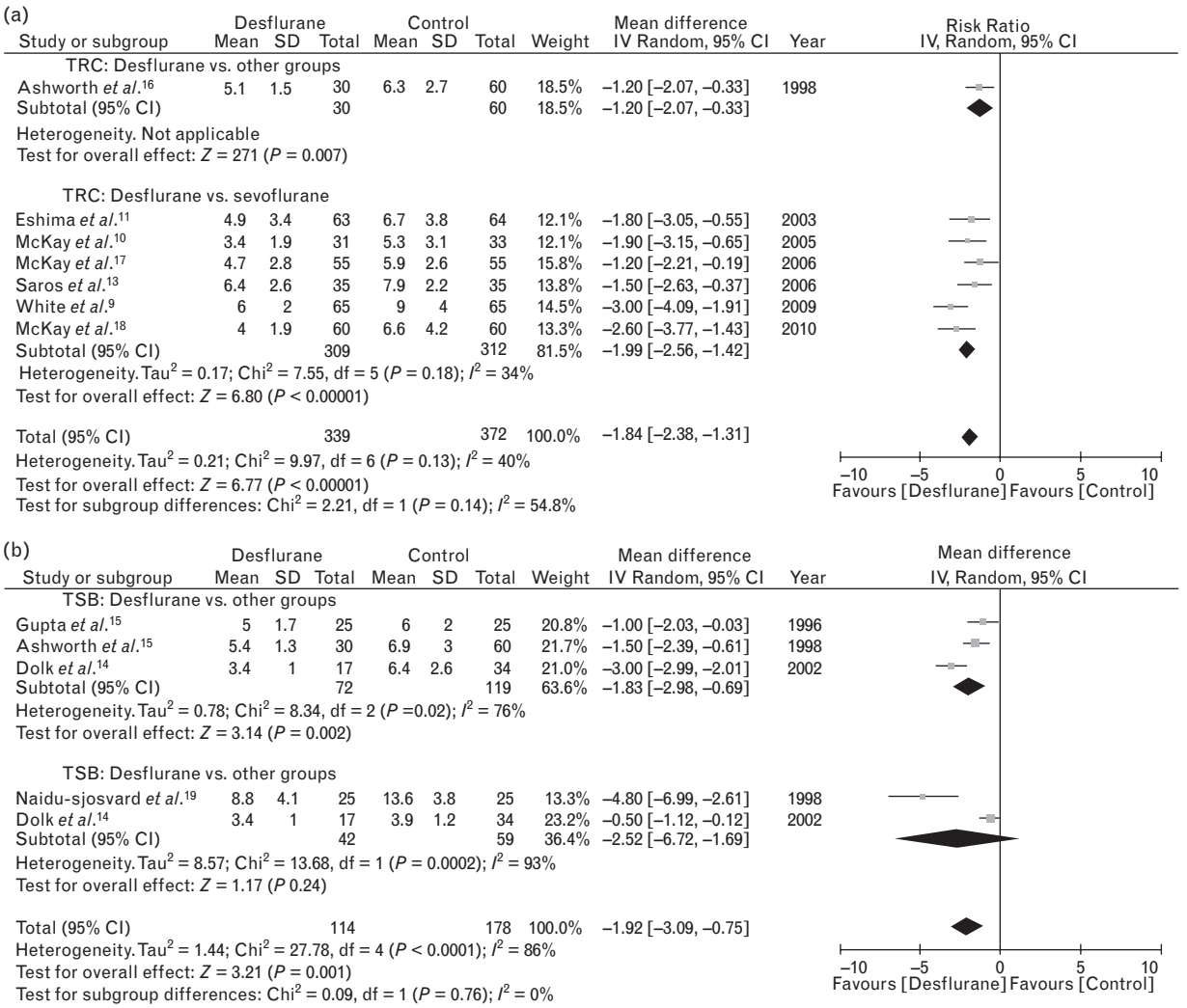
et al.[3] However, for cough at emergence, our result is different. De Oliveira *et al.*[3] found a higher rate of cough at emergence in the desflurane group. This different result is possibly due to different trials being analysed. With respect to cough at emergence, the data analysed by De Oliveira *et al.*[3] came from only three trials. In the current meta-analysis, we included five trials. In addition, we excluded one of the trials,[12] included by De Oliveira *et al.*,[3] as we were unable to extract the relevant data. In that study,[12] which seemed to have the most cough at emergence events, after insertion of the LMA, the inspired volatile concentration was rapidly increased to 2 MAC (minimal alveolar concentration) for all patients as a challenge, rather than on clinical need as in the other studies. Inclusion of this study[12] could have led to bias in the analysis by De Oliveira *et al.*[3] In agreement with Macario *et al*,[21] the emergence times in our study were faster in patients anaesthetized with desflurane.

Patients' characteristics

Use of an LMA instead of tracheal intubation leads to a significantly better haemodynamic stability at anaesthesia induction and during the emergence, which is of particular interest in some American Society of Anaesthesiologists (ASA) III patients. As most of the patients in the trials we analysed were ASA I to II, it remains unclear whether the findings would also apply to ASA III patients. Further RCTs are needed to answer this question.

The proportion of smokers differed between the trials. Cigarette smokers have greater airway irritability and in connection with this an increased risk of intraoperative adverse upper airway events.[22] All participants in one trial[17] were smokers, but those results[17] were similar to the other trials that contained only a small percentage of smokers. Indeed, despite significantly more heavy smokers in the desflurane group, a difference in cough overall

Fig. 5



Forrest plot time to respond to command (TRC) and time to state the date of birth (TSB). Summary mean difference calculated with random effects method for each subgroup shown as subtotals. Summary mean difference calculated with random effects method for desflurane vs. all other agents shown as total. Mean difference for individual studies, square on Forrest plot, with 95% CI of difference, solid line. Diamonds, pooled estimate and uncertainty for the combined effect. Time is represented in minutes. (a) TRC. (b) TSB.

and laryngospasm total was not detected between the desflurane and sevoflurane group.[17] Larger trials including more patients who smoke are required to verify these findings.

Two trials included only women.[6,8] We cannot exclude a potential sex-specific influence on the observed variables in those two trials.[23]

Additional drugs

Additional drugs given before anaesthesia induction or during anaesthesia probably have an important impact on the observed airway events.

Lidocaine is commonly used before anaesthesia induction for the suppression of propofol injection pain.[24] The benefits of intravenous (i.v.) lidocaine on the suppression of upper airway reflexes or on a reduction in the dose of anaesthetic required at induction are controversial.[25] Avoiding i.v lidocaine at induction did not result in a higher rate of laryngospasm total or cough overall (including cough at induction).

The administration of midazolam before induction of anaesthesia not only appears to reduce the required propofol dose but also creates better conditions for LMA insertion, reducing undesirable airway responses.[26,27] The use of preoperative midazolam differed significantly between the trials. Two trials avoided midazolam.[9,16] One reported a much higher rate of cough overall in the desflurane group than sevolfurane,[9] but the other found no

difference in cough overall between desflurane and either isoflurane or propofol.[16] In a trial that observed a significantly higher rate of both cough after induction and cough at emergence in the desflurane group, only a small amount of midazolam was used.[5] It thus remains unclear whether the use of midazolam contributes to a reduction in adverse airway events.

Propofol is known to depress upper airway reflexes.[28] The induction doses used differed significantly, and in some studies, we were unable to determine the propofol dose used for induction. In some trials, additional propofol administered during maintenance anaesthesia was permitted.

Administration of opioids before anaesthesia may influence the occurrence of upper airway reactions. Opioids, also used as antitussives, are known to suppress the central cough reflex.[29] Pretreatment with fentanyl a few minutes before induction significantly reduces the rate of cough and laryngospasm during desflurane anaesthesia[30,31] as well as reducing the propofol requirement for anaesthesia induction.[32] A combination of both, midazolam and opioid, resulted in fewer adverse responses to LMA insertion.[27] One trial reported differences in the occurrence of cough dependent on the opioid. Compared with fentanyl, alfentanil administration before anaesthesia induction led to a much lower rate of cough and laryngospasm at induction.[33] Furthermore the opioid dose also influenced cough occurring after propofol and insertion of LMA.[34,35]

Although we found no significant difference regarding cough overall, one trial did report a manifestly higher rate of cough overall.[9] Of note, in this study,[9] they used neither an opioid nor midazolam pretreatment. Due to different protocols, the opioid dose and the time of administration differed significantly between the trials. In some cases, it is not known how many patients received an opioid. In addition, opioid given before termination of anaesthesia reduces cough at emergence and thus also cough overall.[36]

Independent of any direct central suppression on airway reflexes by opioids, airway irritability due to the pain from the operation site should be kept in mind. We cannot exclude an influence on cough overall by additional analgesia: regional anaesthesia,[17] local anaesthetic wound infiltration at the beginning and the end of the operation,[9] and the intra-articular injection of lidocaine (50 mg) combined with fentanyl (50 μg).[14]

Ventilation mode

The influence of ventilation mode on upper airway reactions in patients with an LMA has not yet been finally determined. It was shown that airway events (including cough at emergence) were comparable between pressure-controlled ventilation and spontaneous breathing.[37] Lema *et al.*[5] observed significantly more cough at both the onset and end of anaesthesia in the desflurane group: the combination of desflurane with controlled ventilation could contribute to this finding. Further studies are needed to evaluate this aspect.

Anaesthetic concentration

For the volatile agents, some trials reported average end-tidal MAC values, some reported average end-tidal concentrations, some reported inspired percentages or MAC values and some did not report any of these. Thus, it was not possible to compare the dose of the volatile agent across the trials. Moreover, it was not possible to relate the doses of propofol in the intravenous anaesthetic techniques[14,16] with inhalational volatile anaesthesia. Another complicating factor was the inconsistent use of N_2O. N_2O is known to reduce the MAC values of volatile anaesthetics.[38] Depending on patient age and N_2O concentration, a reduction in the required desflurane concentration of more than 50% is possible.[39,40] As there were large variations both in the use of N_2O and in the patients' ages, it is important to interpret the reported MAC values and the absolute anaesthetic concentrations with some care. Higher MAC values of volatile agents are required if N_2O is not used and it is known that more than 1 MAC desflurane leads to a higher pulmonary resistance[41] and more adverse events such as coughing.[42]

In three studies comparing desflurane with sevoflurane, without N_2O, the outcomes were contradictory.[5,6,9] Lema *et al.*[5] reported a significantly higher rate of cough at emergence and White *et al.*[9] reported a higher rate of cough overall in the desflurane group: the end-tidal MAC in these studies was 1.0 and 0.8, respectively. On the contrary, de Oliveira *et al.*,[6] using 1 MAC anaesthesia, observed no difference in cough overall and cough at emergence. When N_2O was used, then the end-tidal desflurane concentrations were lower, and there were no significant differences in adverse respiratory events between desflurane and sevoflurane.[16,17] A causal relationship between the use of higher MAC concentrations of desflurane and higher rates of cough at emergence and cough overall cannot be excluded.

With regard to the inter-study age differences, it should be noted that MAC is age dependent: a lower anaesthetic concentration will deliver 1 MAC anaesthesia in patients over 40 years old compared with patients younger than 30 years.

Another consideration is the speed with which a particular depth of anaesthesia was achieved. Rapid increase of desflurane concentration leads not only to a rise in inspiratory resistance and more frequent adverse airway events but also to transient increases in heart rate and blood pressure.[1] In general, there was little information on how quickly desflurane anaesthesia was established in the various studies, so we cannot exclude rapid increases in desflurane concentration at the beginning of anaesthesia, or as an airway challenge,[12] as a factor in the

incidence of coughing or laryngeal spasm. That rapid increases in desflurane may have an impact on cough rates is supported by the study of Lema *et al.*[5] These authors,[5] who observed one of the higher cough rates, administered desflurane with gas flow rates and concentrations predicted by the Gas-Man simulation programme, with the aim of attaining 1 MAC effect site concentration by 8 min. This resulted in 18% desflurane being administered in a 4 l min^{-1} gas flow as soon as the LMA was in place.

Kind of surgery

The procedures differed significantly between the trials (SDC 5, http://links.lww.com/EJA/A58). Only Lema *et al.*[5] studied patients undergoing ear, nose and throat surgery. Due to the close proximity of the LMA and the operation site, mechanical stimulation of upper airway reflexes leading to a higher incidence of cough may explain the high rate of cough at emergence in both groups in this trial compared to the other two trials.[6,9]

We found a substantial difference in the duration of surgery and anaesthesia among the trials and five studies did not report these durations.[6,10,13,17,18] Two trials had a very short procedure time,[8,14] and it is likely that the propofol used for induction of anaesthesia had a greater effect on the observed outcome variables than would be the case in studies with a longer procedure time. Thus, we are unable to determine how anaesthesia duration might impact on the outcomes.

Early recovery

In agreement with previous investigations,[21] we found a substantially faster recovery after desflurane anaesthesia than all other investigated anaesthetic agents (sevoflurane, isoflurane, propofol). All four recovery variables (TOE, TLR, TRC, TSB) showed the same overall result. Faster recovery was even found in obese patients, and after increasing anaesthesia duration.[18] Only one trial failed to show an advantage of desflurane over any other anaesthetic.[16] The reason for this finding remains unclear. One possibility is the short duration of anaesthesia, approximately 24 min. However, other studies with a similar[14] or shorter (18 min)[8] duration found the times to TLR,[14] TSB[14] and TOE[8] were significantly shorter in the desflurane group.

Potential biases and limitations

As we were unable to select at least 10 trials, we did not perform a funnel plot analysis to assess reporting bias across the trials. Publication bias favours trials with positive results[43] and we were unable to identify any trials with negative results that had not been published.[43] We assumed an unclear risk for selective reporting within the trials, as we did not access and analyse the original study protocols. How outcomes were assessed may have varied between trials, as this was not clearly reported in the trials. In addition, we were unable to analyse possible differences in the frequency or severity of the outcomes (cough overall, cough at emergence and laryngospasm total). The variations within study protocols made direct comparisons complicated, and we found a very high heterogeneity in some of our analyses. It is important to note a significantly high risk of detection bias in five trials (Table 3).[13–16,19] The main limitation of this meta-analysis is the small number of participants for many outcomes. As we did not perform Trial Sequential Analysis, we cannot exclude a random error due to a possible inadequate power of our meta-analysis. Accordingly, our results have to be seen within their limits.

Conclusion

In this meta-analysis, the data were insufficient to establish a difference in upper airway adverse events between the groups. A faster recovery in the desflurane group was observed, but how this small time advantage would translate into routine clinical practice is debatable. Due to the dissimilarities in the study protocols, our findings have to be seen within the limitations of the data; thus, additional large RCTs, which clearly define outcome variables and their method of assessment, are indicated.

Acknowledgements relating to this article

Assistance with this article: Non-English manuscripts have been translated by TransPerfect Translation International, Chicago, USA. Baxter International covered translation costs.

Financial support and sponsorship: none.

Conflict of interest: AS declared no conflict of interest. RR, HF, GF, JH, FP, PT and MC have received consulting fees from Baxter Germany to help establish a consensus-based practice recommendation for the use of desflurane with an LMA. MC and RR have ongoing consultancy contracts with AirLiquide and Baxter. MC and RR have clinical trial funding from AirLiquide and Baxter. RR has a research grant from CSL Behring and Boehringer Ingelheim. MC is funded by the DFG (German Research Foundation) for ongoing researches. MC and RR have received payments for lectures (MC: Baxter, AirLiquide; RR: Baxter, CSL Behring and Fresenius). FP is a member of the Advisory Board of Baxter, Germany.

Presentation: none.

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