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Adverse respiratory events with sevoflurane compared with desflurane in ambulatory surgery

A systematic review and meta-analysis

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BACKGROUND An increasing number of studies have concluded that the number of adverse events in the upper airway caused by desflurane does not differ significantly from the number of adverse events caused by sevoflurane. The advantages of desflurane in ambulatory surgery should be reassessed.

OBJECTIVES The aim of this study was to compare adverse respiratory events and recovery outcomes in patients undergoing desflurane or sevoflurane-based anaesthesia in ambulatory surgery.

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

DATA SOURCES A systematic search for eligible RCTs in PubMed, Medline, Cochrane Central Register of Controlled Trials, ScienceDirect and Embase published up to June 2019.

ELIGIBILITY CRITERIA RCTs investigating the occurrence of adverse respiratory events, including airway irritation, stridor, coughing, respiratory distress and laryngospasm, emergence agitation, postoperative nausea and vomiting (PONV), time to eye opening and time to discharge from the operation room after desflurane or sevoflurane-based anaesthesia.

RESULTS Thirteen trials were included and analysed. A total of 634 patients were included in the desflurane group, and 633 patients in the sevoflurane group. The occurrence of respiratory complications was significantly higher with desflurane-based anaesthesia than with sevoflurane-based anaesthesia (Total $n = 673$, 20.0 vs. 12.8%, relative risk (RR) 1.59 (95% CI 1.15 to 2.20)) with low heterogeneity ($I^2 = 20\%$). There was no difference in the occurrence of emergence agitation (Total $n = 626$, 29.1 vs. 27.2%, RR 1.05 (95% CI 0.84 to 1.30)) or the incidence of PONV between the desflurane and sevoflurane groups (Total $n = 989$, 19.0 vs. 21.0%, RR 0.95 (95% CI 0.71 to 1.26)). Time to eye opening was significantly faster with desflurane than that with sevoflurane (Total $n = 1072$, mean difference $= -3.32$ min (95% CI -4.02 to -2.61)) with a substantial heterogeneity ($I^2 = 72.6\%$). There was no significant difference in the time to discharge from the operation room between the two groups (Total $n = 1056$, mean difference $= -0.45$ min (95% CI -5.89 to 4.99)).

CONCLUSION Despite recent reports that there is no significant difference in adverse respiratory events between desflurane and sevoflurane, a pooled analysis revealed that desflurane resulted in a higher rate than sevoflurane. Therefore, the consequences of desflurane should not be neglected and its airway irritant properties should be taken into account.

TRIAL REGISTRATION PROSPERO (CRD42019147939).

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Introduction

The number of ambulatory procedures has increased in the last two decades, primarily owing to rapid medical advances and the desire for cost savings. One vital improvement is the development of anaesthetic agents that maintain stable surgical conditions while allowing a more rapid recovery of consciousness with minimal side-effects.[1] Sevoflurane and desflurane are two of the most widely used volatile anaesthetic agents for ambulatory procedures because of their ideal pharmacokinetic properties and few adverse effects. Factors that may be related to delayed discharge or even unwanted admission include cognitive and cardiovascular recovery, postoperative nausea and vomiting (PONV), postoperative pain and respiratory complications.[2–4] Among these factors, respiratory complications might be the most serious.

The solubility of desflurane in the blood is lower than that of sevoflurane.[5] This results in faster induction and awakening from anaesthesia.[5] However, the irritant properties of desflurane on the airway may provoke increased secretions, coughing, laryngospasm and breath-holding.[6] Accordingly, desflurane is contraindicated for inhalational induction in children.[7,8]

Nonetheless, an increasing number of studies comparing respiratory events between sevoflurane and desflurane-based anaesthesia have concluded that desflurane does not cause significantly more adverse upper airway events than sevoflurane.[9–11] Therefore, this systematic review and meta-analysis of randomised controlled clinical trials (RCTs) aimed to compare differences in the incidence of adverse respiratory events in ambulatory surgery between sevoflurane and desflurane-based anaesthesia.

Materials and methods

Protocol and eligibility criteria

This systematic review and meta-analysis was performed in accordance with the criteria outlined in the PRISMA guidelines.[12] The summary of the PICOS framework that was used to determine eligible articles with primary and secondary outcomes is summarised in Table 1.

Search strategy and study selection

We searched PubMed, Medline, Cochrane Central Register of Controlled Trials, ScienceDirect and Embase databases for qualifying studies that were published up to 30 June 2019 using the following search terms: sevoflurane, desflurane, ambulatory and outpatient. We did not search for ongoing trials, nor proceedings of major annual meetings of anaesthesiology societies.

Two independent reviewers initially screened the titles and excluded duplicated studies or studies that did not meet the eligibility criteria. Studies listed in related systematic reviews or meta-analyses were also screened. A third reviewer was consulted in the event of any disagreements between the first two independent reviewers. The remaining articles were screened by reading the abstract, and potentially eligible trials were analysed in detail by reading the full text. Retrospective studies, case reports, non-English studies, unpublished trials and studies that did not investigate respiratory outcomes were excluded from our analysis.

Data extraction

The full texts of included studies were reviewed by two independent authors. We extracted the following data from the identified articles that met all inclusion criteria: the first author's name, year of publication, type of study, type of surgery, participants' age (adult or child), number of cases in the sevoflurane and desflurane groups, types of intra-operatively accessed airways (mask, laryngeal mask airway or endotracheal tube), special prescription to treat coughing (e.g. fentanyl), PONV and PONV-related factors (e.g. nitrous oxide and prophylactic antiemetics), adverse respiratory outcomes, outcomes related to recovery (time to eye opening, time to discharge from the operation room) and nonrespiratory outcomes (emergence agitation and PONV).

Quality assessment

We assessed the risk of bias by using the Revised Cochrane risk of bias tool for randomised trials (RoB 2.0) that was updated in October 2018.[13,14] This tool assesses the risk of bias via the following six different criteria: allocation bias (bias arising from the randomisation process), performance bias (due to deviation from intended interventions), attrition bias (due to missing outcome), measurement bias (bias in measurement of the outcome), reporting bias (in selection of the reported results) and overall judgement. The two reviewers independently performed the assessment.

Table 1 PICOS framework for studies included in the qualitative synthesis and meta-analysis

PICOS framework	
Participants	Adults or children, elective ambulatory or outpatient surgery, receiving general anaesthesia, nonsedation procedure
Interventions	Maintenance with desflurane
Comparisons	Maintenance with sevoflurane
Outcomes	Primary: adverse respiratory events, including airway irritation, stridor, coughing, respiratory distress, and laryngospasm occurred from intubation to extubation
	Secondary: emergence agitation, postoperative nausea and vomiting, time to eye open, and time to discharge from the operation room
Study Design	Randomised controlled trials with full text in English version

Outcome measures

The major outcome recorded was the occurrence of adverse respiratory events, including airway irritation, stridor, coughing, respiratory distress and laryngospasm. According to each trial's design, all of the respiratory events recorded in the desflurane or sevoflurane groups from induction to extubation were included. Secondary outcomes consisted of emergence agitation, PONV, time to eye opening and time to discharge from the operation room. The definition of emergence agitation depended on the study design of each study and included the incidence of confusion or drowsiness on emergence, 3 or 4 points on the four-point emergence scale, and 4 or 5 points on the five-point agitation score. PONV was recorded, including when it occurred in the postanaesthesia care unit (PACU) and if an antiemetic was given. Nausea took priority over vomiting if they occurred separately during the postoperative period. Time to eye opening was measured as the time elapsed between discontinuing the volatile anaesthetic to the time of eye-opening. Time to discharge from the operation room was measured as the time that elapsed between arrival in the PACU until the time that the criteria for discharge were met. The criteria for discharge depended on each study's design. Study authors were contacted to provide missing data from eligible studies

Statistical analysis

The pooled relative risk (RR) for binary outcomes and the weighted mean difference for continuous outcomes were calculated in this meta-analysis. We obtained standard deviations by dividing the interquartile range by 1.35 and assumed that the median and mean values were identical under a strong assumption of normal distribution. A value of 0.5 was added to each zero cell when the outcome was binary and a zero cell appeared.[15] The data from individual studies were pooled using the DerSimonian and Laird random effect model.[16] The pooled estimates in the child and adult cohorts were compared using a mixed effects model. Next, we performed a subgroup analysis according to several characteristics [the assessed risk of bias, adding fentanyl or not and bispectral index (BIS)] using a mixed effect model to measure the primary outcome (the adverse respiratory events). Interstudy inconsistency was assessed using the I^2 statistic; a value more than 50% indicated substantial heterogeneity.[17,18] Publication bias was detected by a funnel plot[19] and an Egger's test.[20] A sensitivity analysis that evaluated the impact of individual studies was performed by excluding each study one at a time, and the pooled effect size was re-estimated. The risk of bias assessment was performed using Review Manager (RevMan) computer program, version 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014), and the quantitative meta-analysis was conducted using Comprehensive Meta-Analysis version 3.3.070 (Biostat, USA).

A Trial Sequential Analysis (TSA) was performed to further validate the primary and secondary outcomes in the context of information size and effect size using TSA software version 0.9.5.10 beta. The effect size was calculated using the empirical estimate, and conclusions were made according to the following three conditions: required information size, whether the monitoring boundary was crossed and whether the futility boundary was crossed.[21,22] Analyses were two-sided, and the alpha level was set at 5%. In addition, the power was set at 80% in the TSA.

Summary of findings

To assess the quality of the body of evidence associated with the main outcomes, including adverse respiratory events, emergence agitation, PONV, time to eye opening and time to discharge from the operation room, data were exported from Review Manager 5.2 to Guideline development tool (GRADEpro GDT) to create the 'summary of findings' table for the main outcomes. The summary of findings (SoF) was constructed using the GRADE software (Supplemental Table 1, http://links.lww.com/EJA/A409).

Results

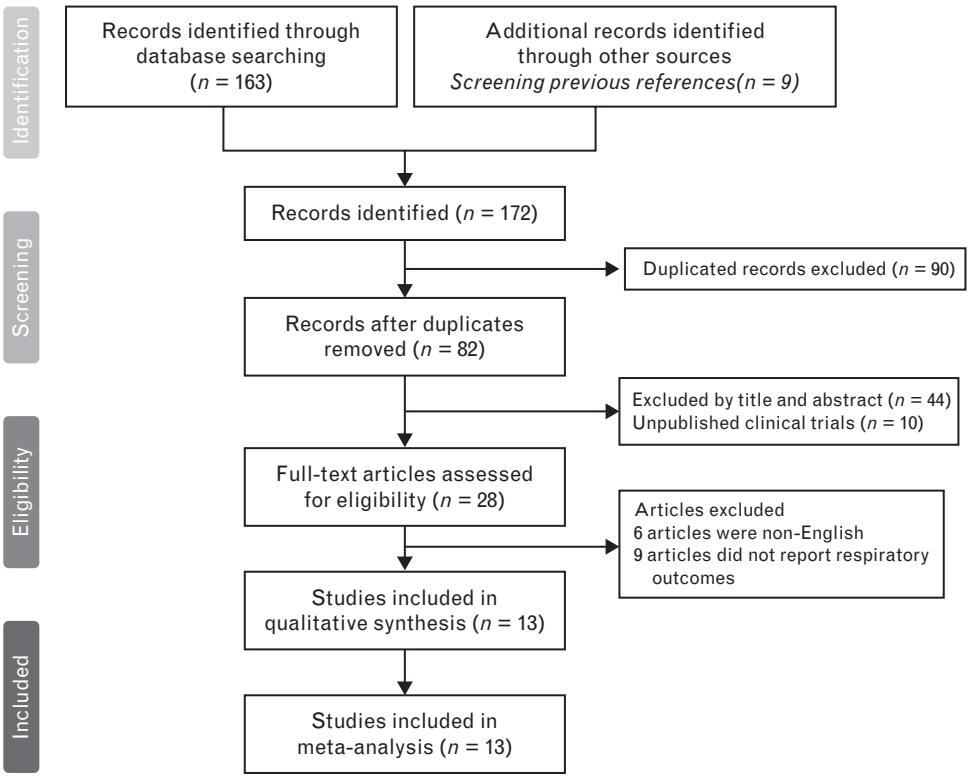
Study selection

Our search strategy yielded a total of 172 trials, including 163 from medical databases and nine from references of previous studies related to our topic. The results did not include registered ongoing trials nor the proceedings of major annual meetings of anaesthesiology societies. After removing duplicates, unpublished trials and articles that did not meet the inclusion criteria based on their title or abstract, we identified 28 potentially eligible publications. Among them, six non-English studies were excluded. After analysing the full text, nine studies that did not investigate respiratory outcomes were also excluded. Thus, 13 randomised controlled trials met our inclusion criteria and were included in our analysis. The search strategy and exclusion process are shown in the flowchart (Fig. 1). Overall, 1267 patients were randomised to receive desflurane or sevoflurane-based anaesthesia (634 and 633 patients, respectively). The characteristics and overview of the selected publications are summarised in Table 2.

Risk of bias

Only two trials met the criteria for low risk of bias.[23,24] Six trials reported random sequence generation and allocation concealment,[23–28] while seven trials did not describe allocation concealment.[29–35] In all of these trials, the clinician who administered the anaesthesia was aware of the type of volatile anaesthetic that was administered, while another individual, who was unaware of the type of anaesthetic that was administered, was responsible for the recording. Two trials had a high risk of performance bias because they lacked a rigid study protocol that may

Fig. 1. PRISMA flowchart of the selection strategy for the meta-analysis



have affected the intra-operative judgement of the anaesthesiologist who was aware of the type of anaesthetic that was administered.[26,27] There was a low risk of performance bias in five trials because of the rigid study protocol, participant adherence, controlled concentration and monitored depth of the volatile anaesthetic.[24,32–34] One trial did not meet the criteria for low risk with regard to attrition bias.[34] One trial had a high risk of measurement bias because the intra-operative measurement was performed by unblinded anaesthetists. Two trials may have had slight measurement bias because it was unclear whether the outcome measurements were recorded by the blinded individuals.[28,30] Four trials did not meet the criteria for low risk of reporting bias because some measurements in the ''Materials and Methods'' section were not completely reported.[25,28,32,35] One trial had a high risk of reporting bias because the data and units in the figure legends and description of the results were inconsistent after the units were converted.[25] With respect to the above potential biases, four trials had a high risk of bias,[25–27,31] while most trials had either a low or unclear risk of bias (Figs. 2 and 3).

Primary outcome: adverse respiratory events

A total of 13 trials with 1267 patients receiving desflurane or sevoflurane-based anaesthesia (634 and 633 patients, respectively) were analysed. Results from the pooled analysis revealed that the occurrence of adverse respiratory events was significantly higher in the desflurane group than in the sevoflurane group (20.0 vs. 12.8%, RR 1.59 (95% CI 1.15 to 2.20), Fig. 4). There was low heterogeneity ($I^2 = 20\%$) among the studies. In addition, the pooled estimates in the adults' and children's cohorts were not significantly different (P for heterogeneity = 0.500). The funnel plot revealed some asymmetry with a significant Egger's test ($P = 0.039$; Supplemental Figure 1, http://links.lww.com/EJA/A410). In addition, the conclusion was not altered when any single study was excluded (data not shown). The TSA revealed that the cumulative Z-curve shortly crossed the trial sequential monitoring boundary but did not exceed the estimated information size. Therefore, the chance of false-positive result may be decreased but it still may exist, and more trials should be included to confirm our findings (Supplemental Figure 2, http://links.lww.com/EJA/A411). The quality of the evidence of adverse respiratory events was low according to the GRADE evaluation (Supplemental Table 1, http://links.lww.com/EJA/A409).

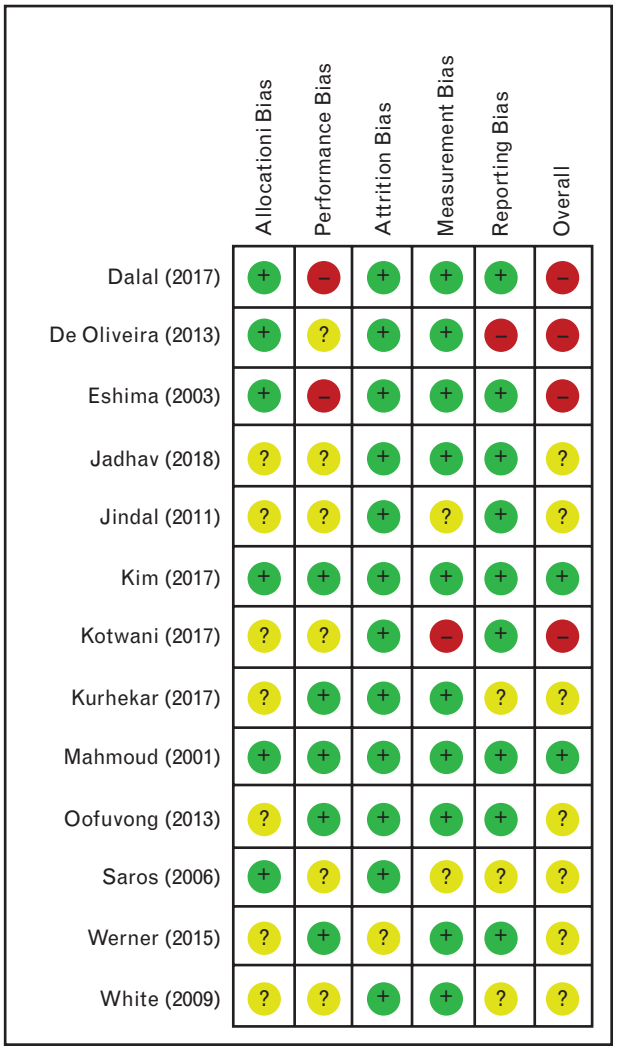
We further conducted a subgroup analysis of 10 trials that included fentanyl prescriptions and three trials that did not include fentanyl. The result showed no significant difference between these two pooled effect sizes (P for heterogeneity = 0.447; Supplemental Figure 3, http://

Table 2 Study characteristics included in the meta-analysis

Ref.	Interventions	Surgical type	Case number	Adults/ Children	Primary outcome	Airway	i.v. Fentanyl	Nitrous oxide	Prophylactic antiemetics	Funding
Mahmoud *et al.*[24]	Desflurane Sevoflurane	Gynaecological day-case surgery	31 vs. 29	Adults	Not specified	LMA	Induction 50 μg	Yes	Metoclopramide	Uncertainty
Eshima *et al.*[27]	Desflurane Sevoflurane	Ambulatory surgery	63 vs. 64	Adults	Incidence of respiratory events	LMA	Intra-operative (dose varied[a])	Yes	No	Baxter[b]
Saros *et al.*[28]	Desflurane Sevoflurane	Varicose veins	35 vs. 35	Adults	Emergence time	LMA	Induction 100 μg	No	Cyclizine Betamethasone	Uncertainty
White *et al.*[35]	Desflurane Sevoflurane	Superficial noncavitary procedure	65 vs. 65	Adults	Overall incidence of coughing	LMA	No	No	Ondansetron Dexamethasone Metoclopramide	Baxter
Jindal *et al.*[30]	Desflurane Sevoflurane	Outpatient laparoscopy gynaecology surgery	50 vs. 50	Adults	Early recovery time	Endotracheal tube	Induction 2 $\mu g\,kg^{-1}$	Yes	No	No
De Oliveira *et al.*[25]	Desflurane Sevoflurane	Outpatient gynaecological hysteroscopy	40 vs. 40	Adults	Time to awakening	LMA	Maintenance 25 μg every 5 min	No	Ondansetron	Baxter
Oofuvong *et al.*[33]	Desflurane Sevoflurane	Ambulatory urologic surgery	68 vs. 68	Children	Incidence of emergence agitation	LMA	Intra-operative 0.5 to 1 $\mu g\,kg^{-1}$	Yes	No	University[c]
Werner *et al.*[34]	Desflurane Sevoflurane	Ambulatory urological cystoscopy	34 vs. 32	Adults	Mean time to eye-opening,	LMA	Induction 1 to 2 $\mu g\,kg^{-1}$	No	No	Baxter
Dalal *et al.*[26]	Desflurane Sevoflurane	Hysteroscopic gynaecological surgery	45 vs. 47	Adults	Adverse airway events	LMA	Premedication 1 $\mu g\,kg^{-1}$	Yes	Ondansetron	No
Kim *et al.*[23]	Desflurane Sevoflurane	Ambulatory strabismus surgery	100 vs. 100	Children	Overall incidence of adverse respiratory events	LMA	No	No	No	No
Kotwani *et al.*[31]	Desflurane Sevoflurane	Ambulatory lower abdominal surgery	30 vs. 30	Children	not specified	LMA	No	Yes	No	No
Kurhekar *et al.*[32]	Isoflurane Sevoflurane Desflurane	Ambulatory surgery	34 vs. 33 vs. 33	Adults	Time from immediate recovery to home readiness	LMA	Induction 2 $\mu g\,kg^{-1}$	Yes	Ondansetron	No
Jadhav *et al.*[29]	Desflurane Sevoflurane	Elective short surgical procedures	40 vs. 40	Adults	Early postoperative recovery profile	LMA	Premedication 2 $\mu g\,kg^{-1}$	Yes	Ondansetron Dexamethasone	No

[a] Eshima *et al.*[27]: The attending anaesthesiologist added fentanyl to the induction regimen based on clinical circumstances. Total mean ± SD intra-operative fentanyl use was 141 ± 108 μg in Desflurane group and 129 ± 118 μg in Sevoflurane group. [b] Baxter: Baxter Healthcare Corporation, Deerfield, Illinois, USA. [c] Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand.

Fig. 2. Risk of bias summary of the eligible studies



links.lww.com/EJA/A412), indicating the observed effect was similar between the trials with fentanyl prescriptions (13.9 vs. 7.3%, RR 1.79 (95% CI 1.14 to 2.81), $I^2 = 0\%$) and those trials without fentanyl prescriptions (33.8 vs. 25.1%, RR 1.39 (95% CI 0.87 to 2.22), $I^2 = 60.8\%$). We also conducted a subgroup analysis of 10 trials that included adults and three trials that included children. The result showed no significant difference between these two pooled effect sizes (P for heterogeneity = 0.500; Fig. 4), indicating the observed effect was similar between the adults (14.9 vs. 8.0%, RR 1.75 (95% CI 1.14 to 2.71), $I^2 = 0\%$) and the children (31.3 vs. 23.2%, RR 1.40 (95% CI 0.86 to 2.29), $I^2 = 62.5\%$). An additional subgroup analysis of the primary outcome (adverse respiratory events) according to the assessed risk of bias (low vs. high or unclear risk) was performed, and the pooled effect size was substantially smaller in the two studies with lower risk of bias than the pooled effect size in the 11 studies with higher or unclear risks of bias (P for heterogeneity = 0.017; High or unclear risk group: 16.1 vs. 7.7%, RR 1.95 (95% CI 1.36 to 2.80), $I^2 = 0\%$; Low risk group: 35.1 vs. 32.6%, RR 1.08 (95% CI 0.77 to 1.50), $I^2 = 0\%$; Supplemental Figure 4, http://links.lww.com/EJA/A413). The subgroup analysis of the BIS group and non-BIS group showed that, in the BIS-guided subgroup, there were significantly more adverse respiratory events in the desflurane group (non-BIS group: 18.6 vs. 13.5%, RR 1.24 (95% CI 0.95 to 1.63), $I^2 = 13.3\%$; BIS group: 25.2 vs. 10.2%, RR 2.36 (95% CI 1.36 to 4.09), $I^2 = 0\%$; P for heterogeneity = 0.042, Supplemental Figure 12, http://links.lww.com/EJA/A421).

Secondary outcomes

Emergence agitation

We analysed emergence agitation in five trials that included 626 patients who were administered desflurane or sevoflurane-based anaesthesia (313 patients each). Results from the pooled analysis revealed that there was no significant difference in the occurrence of

Fig. 3. Risk of bias graph of the eligible studies

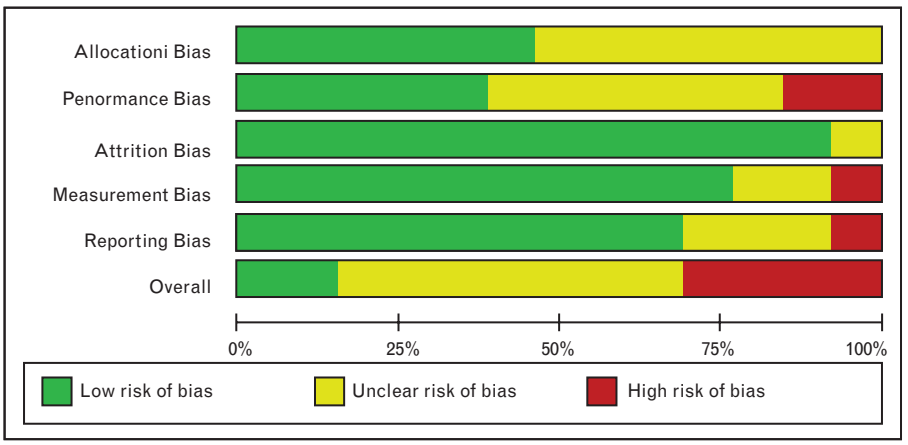
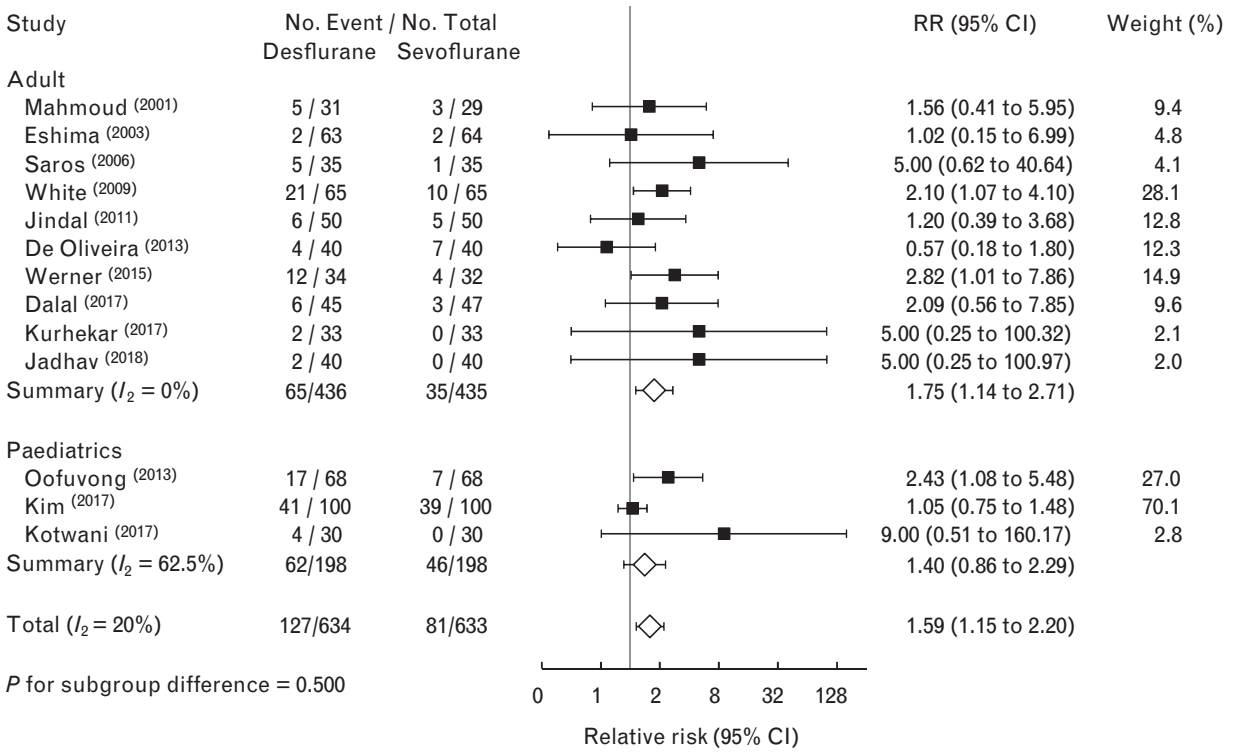


Fig. 4. Forest plot of adverse respiratory events for desflurane-based and sevoflurane-based anaesthesia



emergence agitation between the desflurane and sevoflurane groups: 29.1 vs. 27.2%, RR 1.05 (95% CI 0.84 to 1.30), and the heterogeneity was low ($I^2 = 0\%$) (Fig. 5). In addition, the pooled estimates in the adults' and children's cohorts were not significantly different (P for heterogeneity = 0.602), indicating that the observed effect was similar between the adults and the children. The funnel plot revealed some asymmetry with a significant Egger's test ($P = 0.032$; Supplemental Figure 5, http://links.lww.com/EJA/A414). In addition, the conclusion was not altered when any one of the single studies was excluded (data not shown). We were unable to calculate the boundary TSA, which was ignored due to too little information (3.56%). The quality of the

Fig. 5. Forest plot of emergence agitation for desflurane-based and sevoflurane-based anaesthesia

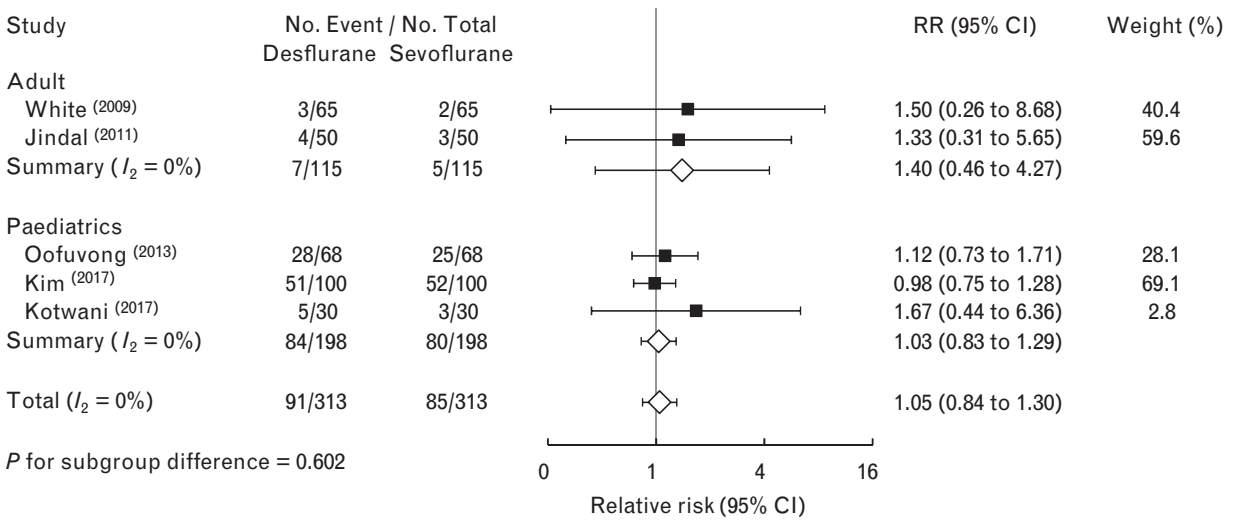
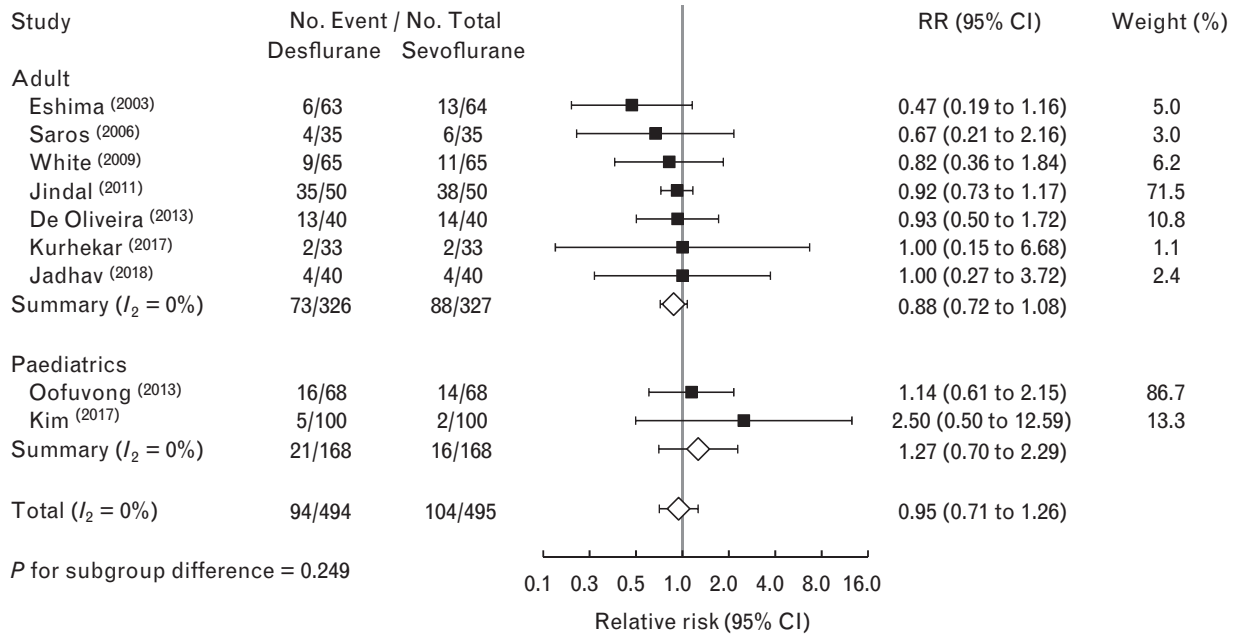


Fig. 6. Forest plot of postoperative nausea and vomiting for desflurane-based and sevoflurane-based anaesthesia



evidence of emergence agitation was low according to the GRADE evaluation (Supplemental Table 1, http://links.lww.com/EJA/A409).

Postoperative nausea and vomiting

We analysed PONV in nine trials that included 989 patients who were administered desflurane or sevoflurane-based anaesthesia (494 and 495 patients, respectively). There was no significant difference in the incidence of PONV between the two volatile anaesthetics (19.0 vs. 21.0%, RR 0.95 (95% CI 0.71 to 1.26)), and the heterogeneity was low ($I^2 = 0\%$) (Fig. 6). In addition, the pooled estimates in the adults' and children's cohorts were not significantly different (P for heterogeneity = 0.249), indicating that the observed effect was similar between the adults and the children. The funnel plot was generally symmetric with a nonsignificant Egger's test ($P = 0.985$; Supplemental Figure 6, http://links.lww.com/EJA/A415). In addition, the conclusion was not altered when any one of the single studies was excluded (data not shown). The quality of the evidence of PONV was low according to the GRADE evaluation. The TSA demonstrated that the cumulative Z-curve did not cross the trial sequential monitoring boundary and the estimated information size; therefore, our analysis may have generated false-negative findings, and more trials should be included to confirm our conclusions (Supplemental Figure 7, http://links.lww.com/EJA/A416). The subgroup analysis of the prescription of nitrous oxide or prophylactic antiemetics did not change the main finding (data not shown).

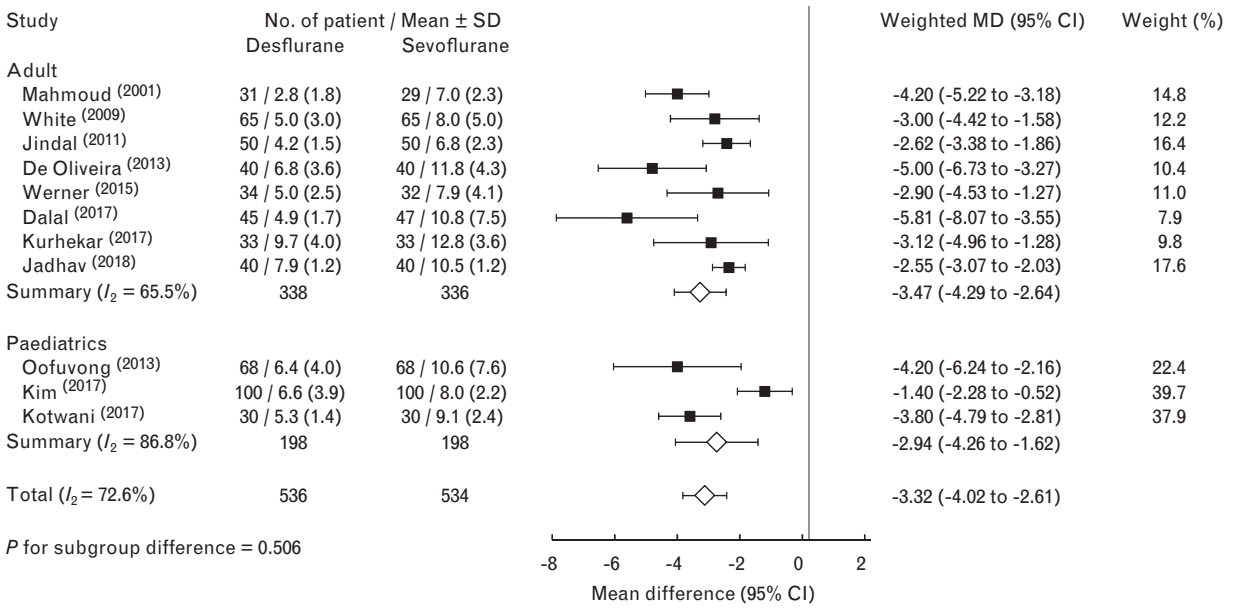
Time to eye opening

We analysed the time to eye opening in 11 trials that included 1070 patients who were administered desflurane or sevoflurane-based anaesthesia (536 and 534 patients, respectively). The time to eye opening was significantly shorter in the desflurane than in the sevoflurane group (mean difference = −3.32 min (95% CI −4.02 to −2.61), Fig. 7), and the heterogeneity was substantial ($I^2 = 72.6\%$). In addition, the pooled estimates in the adults' and children's cohorts were not significantly different (P for heterogeneity = 0.506), indicating the observed effect was similar between the trials. The funnel plot revealed some asymmetry with a borderline significant Egger's test ($P = 0.055$; Supplemental Figure 8, http://links.lww.com/EJA/A417). In addition, the conclusion was not altered when any one of the single studies was excluded (data not shown). The TSA indicated that the cumulative Z-curve crossed the trial sequential monitoring boundary and exceeded the estimated information size; therefore, our conclusion was sufficient and no more trials are needed to confirm our conclusions (Supplemental Figure 9, http://links.lww.com/EJA/A418). The quality of the evidence of time to eye opening was very low according to the GRADE evaluation (Supplemental Table 1, http://links.lww.com/EJA/A409).

Time to discharge from operation room

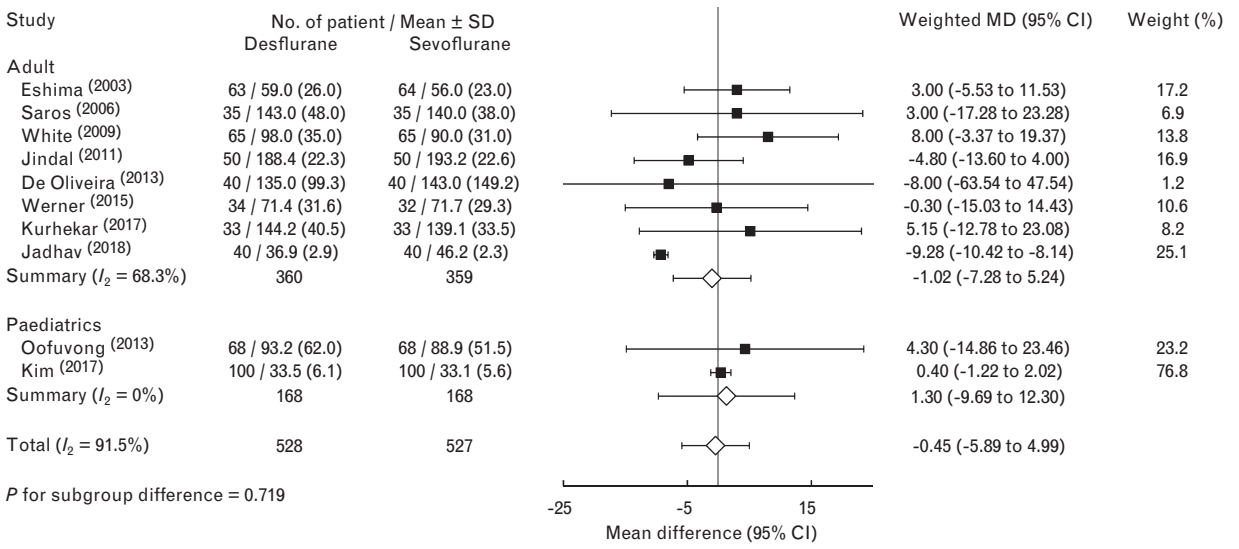
We analysed the time to discharge from the operation room in 10 trials that included 1055 patients who were administered desflurane or sevoflurane-based anaesthesia (528 and 527 patients, respectively). There was no

Fig. 7. Forest plot of time to eye open for desflurane-based and sevoflurane-based anaesthesia



significant difference in the time to discharge from the operation room between the two anaesthetic agents (mean difference = -0.45 min, 95% CI -5.89 to 4.99), and the heterogeneity was substantial (I^2 = 91.5, Fig. 8). In addition, the pooled estimates in the adults' and children's cohorts were not significantly different (P for heterogeneity = 0.719) indicating the observed effect was similar between the trials. The funnel plot was generally symmetric with a nonsignificant Egger's test (P = 0.985; Supplemental Figure 10, http://links.lww.com/EJA/A419). In addition, the conclusion was not altered when any one of the single studies was excluded (data not shown). The quality of the evidence of time to discharge from the operation room was very low according to the GRADE evaluation (Supplemental Table 1, http://links.lww.com/EJA/A409). The TSA showed that the cumulative Z-curve did not cross the trial sequential monitoring boundary and the estimated information size; therefore, our analysis may have generated false-negative findings, and more trials should be included to confirm our conclusions (Supplemental Figure 11, http://links.lww.com/EJA/A420).

Fig. 8. Forest plot of time to discharge from operation room for desflurane-based and sevoflurane-based anaesthesia



Discussion

The number of ambulatory procedures has rapidly increased over the past few decades. Sevoflurane and desflurane are the two most popular volatile anaesthetics used during ambulatory surgery. Although recent publications have revealed that there is no significant difference in the incidence of upper airway events between desflurane and sevoflurane during the maintenance of general anaesthesia, results from this meta-analysis indicate that the risk of respiratory events was increased and the time to eye opening was decreased in patients who were administered desflurane compared with those who were administered sevoflurane during ambulatory surgery.[9–11] This meta-analysis reveals that, compared with sevoflurane, using desflurane in ambulatory surgery increases the overall risk of respiratory events and decreases the time to eye opening on a large sample pool analysis. However, our results also revealed that there were no differences in emergence agitation, PONV or time to discharge from the operation room between the desflurane and sevoflurane groups.

Stevanovic *et al.*[11] and De Oliveira *et al.*[9] also conducted meta-analyses on this topic. In their respective studies, Stevanovic *et al.*[11] pooled 13 studies that included 1143 individuals who were administered desflurane or other anaesthetics during general anaesthesia with laryngeal mask. De Oliveira *et al.*[9] pooled seven studies that included 657 individuals who were administered desflurane or sevoflurane during general anaesthesia with LMA. In our present study, we pooled 13 studies that included 1267 patients with an emphasis on the differences between desflurane and sevoflurane in ambulatory surgery. Although Stevanovic *et al.*[11] mentioned that the occurrence of airway events was higher in the desflurane group than in the sevoflurane group, these differences were not statistically significant. We evaluated the latest publications in the present meta-analysis, and this resulted in the inclusion of more studies and study subjects than ever before.

Contrary to the findings presented by De Oliveira *et al.*[9] and Stevanovic *et al.*,[11] our meta-analysis revealed that the overall number of respiratory events was higher in the desflurane group than in the sevoflurane group. The incidence of coughing, laryngospasm and cough was significantly higher in the desflurane group of De Oliveira *et al.*[9] On the basis of an asymmetric funnel plot that indicated the possibility of publication bias, De Oliveira *et al.*[9] were unable to demonstrate that the incidence of upper airway adverse events was higher in the desflurane group than in the sevoflurane group. The included trial conducted by De Oliveira *et al.*[25] was the only one that exhibited opposite results with regard to respiratory events (Fig. 4) and had a moderate risk of reporting bias and a high risk of performance bias (Figs. 2 and 3).

In this study, we evaluated the occurrence of respiratory events from induction until extubation. The definition of adverse respiratory events in our study design is more relevant to clinical practice and reminds clinicians that the airway irritation properties of desflurane should not be neglected or underestimated, especially during ambulatory surgery. Clinicians should be aware of the higher risks of peri-anaesthetic airway events in desflurane-based anaesthesia compared with sevoflurane and should also be well prepared to prevent such incidents. The subgroup analysis of the main outcome in the adult and laryngeal mask group revealed similar conclusions; however, there were no significant differences in the paediatric group and endotracheal tube group. The lack of statistical significance in these groups may be explained by the small sample size and paucity of past studies. Premedicating with fentanyl leads to coughing,[36] which may interrupt the recording of airway events. In our study, the use of a subgroup analysis clarified these concerns, and the results were consistent in patients who were and who were not premedicated with fentanyl. The testing of subgroup differences according to adults/children, and fentanyl prescription were insignificant, and the result for adverse respiratory events applied to both adults and children, with or without prescribing fentanyl. However, the subgroup analysis according to risk of bias and BIS-guidance were significant. Therefore, our research results are not applicable to these groups.

The PONV rate was not different between the desflurane and sevoflurane groups, including the adults' and children's groups. Results from a previous study revealed that the incidence of PONV was higher when volatile anaesthetics were used than that when propofol total intravenous anaesthesia was used.[37] In recent retrospective studies, the use of desflurane was identified as an independent risk factor for the development of PONV in adults,[38] and results from a propensity score matching analysis revealed that the rate of PONV was lower in patients who were administered sevoflurane than those given desflurane during thyroidectomy.[39] Our present meta-analysis was not able to adequately respond to the above studies; the prescription of antiemetics in the included trials was not in accordance with recommendations for clinical practice.[40] A previous study reported that antiemetic prophylaxis resulted in a significant reduction in the incidence of PONV[41]; therefore, the use of antiemetics may have influenced the incidence of PONV in the current study. Even though the use of nitrous oxide and prophylactic antiemetics is known to affect the occurrence of PONV, results from the subgroup analyses revealed that the use of prophylactic antiemetics and nitrous oxide had little to no effect on the rate of PONV in our study (data not shown).

Consistent with previously published studies, this meta-analysis also revealed that the time to eye opening was decreased in the desflurane group compared with the sevoflurane group.[9,11,42] Rapid recovery from desflurane anaesthesia in both adults and children has been

generally acknowledged. We found that the mean difference in the time to eye opening between the desflurane and the sevoflurane group was 3.12 (95% CI, 2.50 to 3.75) min. Although statistically significant, the mean difference was not more than 5 min in present and previous meta-analyses.[11,42] According to the analysis of subgroup differences, the results for emergence agitation, PONV, time to eye opening and time to discharge from the operation room are applicable to both adults and children.

Although desflurane is associated with an increased number of adverse respiratory events and decreased time to eye opening, the time between arriving on the PACU to discharge was similar to that in the sevoflurane group; the increased time to eye opening that was associated with sevoflurane did not affect the time spent in the PACU. Oofuvong *et al.*[33] reported that one surgery-related unplanned admission was observed in the sevoflurane group and three surgery-related unplanned admissions were observed in the desflurane group. Two anaesthesia-related unplanned admissions were seen in both groups, and one child from the sevoflurane group had a pulmonary aspiration with desaturation that resolved within two days. No permanent or serious adverse events were observed in any of the other participants.

Limitations

This study had multiple limitations. First, we restricted the study selection to English language journals, and this may have been a potential source of bias that overestimated of the treatment effect. According to Laura McAuley *et al.*,[43] positive results are more frequently published in English-language journal than negative results. Therefore, the omission non-English language studies may have also overestimated the treatment effect. Second, many factors that may influence the potential ventilatory side effects of desflurane, such as the use of BIS monitoring,[44,45] and multimodal analgesia, were not investigated in our study. Third, publication bias was observed in the primary outcome and some of the secondary outcomes, including emergence agitation and time to eye opening, and some biases, such as drugs used for induction, the use of NSAIDs, lidocaine, alpha-2 agonists and muscle relaxants, and the age of children were not evaluated.[46] Fourth, results from the time to eye opening and discharge were limited by significant heterogeneity; therefore, these results may be less reliable than originally expected.[47] Fifth, this study compared desflurane and sevoflurane in ambulatory surgery; we did not make any comparisons with isoflurane nor did we assess the use of propofol in different types of surgical procedures. Sixth, there may have been some bias resulting from the fact that the overall respiratory events that occurred between induction and extubation depended on various study designs and definitions, including the fact that the recovery profiles that were used to evaluate the time to discharge from operation room varied according to the study. Seventh, adults and children have different pathophysiological manifestations and different incidence rates of airway events, emergence agitation, and PONV even though a subgroup analysis on each outcome had been performed. Results from this study should be applied to clinical practice with caution, and individual differences, surgical types and the advantages and disadvantages of the different volatile anaesthetics should be taken into consideration before the induction of anaesthesia. Further randomised controlled clinical studies are required to confirm the current findings and devise better treatment plans for patients undergoing ambulatory surgery.

Conclusion

Results from our meta-analysis revealed that the number of adverse respiratory events was increased and the time to eye opening was decreased in patients who were administered desflurane compared with sevoflurane during ambulatory surgery. Despite recently published reports that the incidence rate of adverse respiratory events was not significantly different between desflurane and sevoflurane, we observed statistically significant differences in the incidence of adverse respiratory events between the two anaesthetics. Although desflurane is associated with a fast recovery rate, the occurrence of respiratory events should not be neglected and its airway irritant properties should be taken into account. In the future, anaesthesiologists should consider the advantages and disadvantages of each drug when selecting anaesthetics for ambulatory anaesthesia.

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