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A review of recovery from sevoflurane anaesthesia: Comparisons with isoflurane and propofol including meta-analysis

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Background: Sevoflurane has a lower blood:gas partition coefficient than isoflurane and thus should be associated with a more rapid recovery from anaesthesia.
Methods: A review and meta-analysis were employed to examine the recovery profiles of adult patients following anaesthesia, comparing sevoflurane to isoflurane and sevoflurane to propofol.
Results: There were significant differences in times to several recovery events that favoured sevoflurane to isoflurane anaesthesia, including time to emergence, response to commands, extubation, and orientation. Likewise, there were significant differences in times to the same recovery events following anaesthesia with sevoflurane versus propofol. There were no differences in time to recovery room discharge when comparing sevoflurane to isoflurane or propofol.
Conclusion: The observed differences between sevoflurane and isoflurane or propofol anaesthesia support the postulate that the use of sevoflurane is associated with a more rapid recovery from anaesthesia than either isoflurane or propofol.

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Key words: Anesthesia recovery period; anesthetics, intravenous; propofol; anesthetics, volatile: isoflurane, sevoflurane; statistics: meta analysis.

SEVOFLURANE is a volatile anaesthetic with a low blood:gas partition coefficient (0.65) (1). It would be expected that anaesthesia using sevoflurane would reduce the time intervals from stopping the delivery of the anaesthetic to specific emergence and recovery parameters (e.g., time to extubation, emergence, orientation, etc.) when compared to anaesthesia using volatile agents with higher blood:gas partition coefficients (e.g., isoflurane, enflurane). This insolubility might also permit more rapid and predictable recovery endpoints compared to intravenous anaesthesia with propofol. Not surprisingly, many, but not all, published studies have demonstrated statistically significant reductions in these recovery parameters when comparing anaesthesia with sevoflurane to that with isoflurane (2–9) or propofol (10–13).

Although most of these studies demonstrate statistically significant differences, the clinical significance, i.e., the improvement in recovery when using sevoflurane compared with the other anaesthetic agents, cannot always be conclusively demonstrated within these individual studies. This is because the confidence of calculating an effect of using one treatment compared to another (e.g., the reduction in time to emergence following sevoflurane anaesthesia versus isoflurane anaesthesia) is often compromised by the relatively small sample sizes within studies or by differences in study populations that lead to inconsistent results. However, by using meta-analysis and pooling the results of several studies which use similar criteria and outcome measurements, sample sizes can be substantially increased, although new confounding factors may be added. This narrows the confidence intervals of the outcome measurements when comparing different anaesthetics. Conclusions can thus be reached regarding the efficacy of drug treatment with greater confidence than any single study can offer (14).

Meta-analysis applied to a common parameter (e.g., emergence) can provide the mean difference of two treatments (e.g., two anaesthetic agents) and can provide the confidence intervals of this mean difference. A 95% confidence interval that does not include zero is equivalent to a statistically significant difference at the 0.05 level of significance. In this study we used meta-analysis to compare the times to specific recov-

ery events in adult patients anesthetized with an intravenous anesthetic and receiving sevoflurane to similar patients receiving isoflurane or propofol for elective surgical procedures that would typically be associated with routine tracheal extubation at the end of the procedure.

Methods

The Medline database was searched between 1966 and July, 1998, to identify manuscripts in English, limited to human studies, which included the text words ''sevoflurane'' and ''isoflurane''or ''propofol'' and ''interval,'' ''time,'' ''duration,'' ''recovery'' or ''emergence.'' Studies identified and used in the meta-analysis are summarized in Tables 1 and 2.

For individual studies to be included in the meta-analysis, the following criteria were established: patients were adult (≥18 yr), had intravenous induction, were randomly assigned to receive sevoflurane or the other maintenance agent (isoflurane or propofol), and extubation was planned at the end of surgery.

The following recovery outcomes (i.e., treatment effect variables) were identified after the literature search:

1. Emergence: time from discontinuation of anaesthesia delivery (i.e., vaporizer or propofol infusion pump turned off) to open eyes;
2. Extubation: time from discontinuation of anaesthesia delivery to endotracheal extubation;
3. Response to commands: time from discontinuation of anaesthesia delivery to response to verbal commands (e.g., hand squeeze);
4. Orientation: time from discontinuation of anaesthesia delivery to orientation (e.g., date of birth);
5. First analgesic: time from discontinuation of anaesthesia delivery to first post-operative analgesic; and
6. Recovery discharge: time from discontinuation of anaesthesia delivery to eligibility for discharge from recovery room.

The meta-analysis of the times to recovery events calculated the confidence intervals for the pooled mean differences between sevoflurane and isoflurane or propofol. A 95% confidence interval that did not include zero was equivalent to a statistical difference at the 0.05 level of significance (14).

Results

A total of 18 published studies were compatible with the inclusion criteria, and all studies but one (2) included 60–70% N_2O in the inspired gas mixture.

Table 1

Summary of studies comparing sevoflurane and isoflurane.

Study	Number	Age Range	ASA Class	MAC Hours		End-tidal concentration (%)		Duration (min)	
				Sevo	Iso	Sevo	Iso	Sevo	Iso
Frink et al. (3)	49/25	42±13/42±12	I, II	2.5±1.1	2.7±1.2	2.1±0.06	1.3±0.07	–	–
Smith et al. (2)	25/25	44±12/46±12	I, II	–	–	0.86±0.35	0.77±0.28	154±59	153±53
Quinn et al. (5)(Gyn)	15/15	41±6/50±12	I, II	0.66±0.31	0.88±0.39	0.86±0.27	0.58±0.23	65±12	72±15
Quinn et al. (5)(Ab)	10/10	63±21/71±11	I–III	0.99±0.60	1.49±0.54	0.66±0.13	0.41±0.06	177±92	196±47
DeSouza et al. (6)	21/19	73±6/70±4	–	–	–	–	–	180–240	
Philip et al. (9)	149/97	33±9/35±10	I–III	0.6±0.48	0.8±0.49	1.44±0.49	0.83±0.20	50±37	60±39
Scholz et al. (16)	247/253	36±12/36±12	I–III	0.64±0.47	0.66±0.48	1.25±0.63	0.98±0.48	46±31	47±32
O'Hara et al. (17)	25/22	35±6/34±6	I, II	–	–	1.54±0.40	0.95±0.38	84±35	67±38
Campbell et al. (18)	272/283	43±16/42±16	I–III	1.52±1.6	1.58±1.7	1.23±0.33	0.79±0.34	131±66	134±67
Eriksson et al. (8)	24/25	30±4/32±5	I, II	–	–	0.4 (0.2–0.7)	0.3 (0.2–0.7)	41±20	40±26
Campbell et al. (15)	24/26	45±15/51±14	I–III	1.4±0.5	1.6±0.5	1.3	0.8	139±57	147±57
Cantillo et al. (19)	23/27	53±18/56±17	I–III			2, to effect	1.4	142±67	105±67
Wiesner et al. (4)	26/24	42/36	I, II	1.2 (0.5–4.2)	1.3 (0.6–3.0)	0.82 (0.47–1.28)	0.59 (0.41–0.97)	106 (40–300)	114 (52–262)

Data are shown as mean±SD. */:* separates data for sevoflurane/isoflurane groups.

Table 2

Summary of studies comparing sevoflurane and propofol.

Study	Number	Age range	ASA class	Sevoflurane ETconc.%	Propofol Infusion rate $\mu g \cdot kg^{-1} \cdot min^{-1}$	Anaesthesia duration (min)	
						Sevoflurane	Propofol
Dubin et al. (21)	143/143	18–75/18–71	I–III				
Huang et al. (10)	27/26	35±11/34±9	I, II	2	100–150	95±43	95±43
Wandel et al. (12)	25/25	41±16/36±14	I, II	1–3	100–200	45±27	54±23
Fredman et al. (11)	48/50	36±12/37±12	I, II	1.51±0.36	135±6	78±28	74±29
Ræder et al. (23)	84/85	32±10/33±9	I, II	1.41±0.37	133±36	48±2	44±2
Jellish et al. (13)	93/93	44±13/42±14	I, II			132±67	134±67
Song et al. (20)	40/40	27±5/28±5	I, II	1.04±0.5	81±23	69±22	69±26

Data are shown as mean±SD. /: separates data for sevoflurane/propofol groups.
ETconc=end-tidal concentration.

Twelve studies comparing sevoflurane to isoflurane were identified (2–6, 8, 9, 15–19). Two of these (4, 8) did not report mean data with standard deviation or error of the mean and could not be included in the meta-analysis. Data from two other studies (15, 19) were included in one summary of a multicentre study (18) and were therefore excluded from analysis. One study (5) comprised two surgical groups which were included as separate studies in the meta-analysis. In addition, seven published studies comparing sevoflurane to propofol were identified (10–13, 20, 21, 23). Two published studies were duplicates (12, 22) and therefore only one set of results (12) was included in the meta-analysis. One excluded study was an abstract (10) reporting on a small number of patients, who were also included in the summary statistics of the multicentre report (21). One sevoflurane vs. propofol report, a summary of a multicentre study involving 186 patients (13), could not be used in the meta-analysis because we included only studies where anaesthesia was induced with an intravenous agent.

The results of the meta-analysis of the published studies which compared sevoflurane to isoflurane are summarized in Table 3. There were statistically significant differences in the pooled data between sevoflurane and isoflurane in the times of emergence (Fig. 1), endotracheal extubation, response to commands, orientation and first post-operative analgesic, but not in times to recovery room discharge. The results of the meta-analysis of the published studies which compared sevoflurane to propofol are summarized in Table 4. There were statistically significant differences in the pooled data between sevoflurane and propofol in the times of emergence (Fig. 2), endotracheal extubation, response to commands and orientation, but not in times to recovery room discharge.

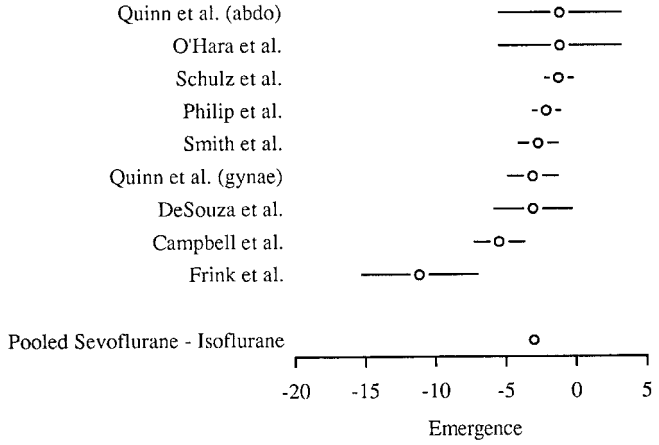

Fig. 1. The difference between sevoflurane and isoflurane (sevoflurane minus *isoflurane) on emergence time. Data are shown as the mean differences (open circles) and 95% confidence intervals (horizontal lines) for the individual studies, and pooled data.*

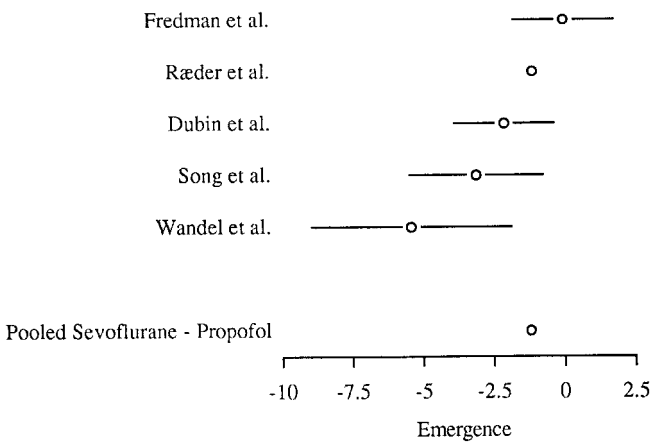

Fig. 2. The difference between sevoflurane and propofol (sevoflurane minus *propofol) on emergence time. Data are shown as the mean differences (open circles) and 95% confidence intervals (horizontal lines) for the individual studies, and pooled data.*

Table 3

Differences of the mean data between sevoflurane and isoflurane from published studies.

	Differences in time (min)					
Study Event:	Emergence	Response to commands	Extubation	Orientation	First analgesic	Discharge from recovery room
Frink et al. (3)	−11.1±2.1	–	–	–	−10.6±2.3	–
Smith et al. (2)	−2.6±0.7	−3.2±0.9	−2.6±0.7	−3.9±1.2	–	9.0±12.9
Quinn et al. (5)(Gyn)	−3.0±0.9	−5.0±1.8	−3.0±0.9	−7.0±2.7	–	–
Quinn et al. (5)(Ab)	−1.0±2.2	−3.0 ±2.5	−2.0 ±2.0	−9.0±5.3	–	–
DeSouza et al. (6)	−3.0±1.4	−7.0±3.2	−4.0±2.2	−12.0±2.9	–	–
Philip et al. (9)	−2.0±0.5	−2.0±0.5	−1.0±0.4	−3.0±0.6	−3.0±4.2	−7.0±2.4
Scholz et al. (16)	−1.1±0.5	−1.3±0.5	−4.0±6.2	−2.4±0.7	−13.2±7.7	8.5±7.4
O'Hara et al. (17)	−1.0±2.2	–	–	−3.4±1.9	–	13.8±10.7
Campbell et al. (18)	−5.4±0.9	−5.6±1.0	5.0±4.2	−7.5±1.3	−9.3±4.4	−26.7±22.6
Pooled data						
Mean	−2.9±0.1	−3.0±0.2	−1.6±0.1	−4.5±0.2	−8.9±1.0	0.7±1.7
Confidence interval	−3.1 to −2.7	−3.3 to −2.7	−1.9 to −1.3	−4.8 to −4.2	−10.8 to −7.0	−2.7 to 4.1

Number of subjects in sevoflurane/isoflurane groups on Table 1. Differences in time are the mean sevoflurane time minus the mean isoflurane time. Differences are reported as mean±pooled variance. −: data not collected.

Table 4

Differences of the mean data between sevoflurane and propofol from published studies.

	Differences in time (min)				
Study Event:	Emergence	Response to commands	Extubation	Orientation	Discharge from recovery room
Dubin et al. (21)	−2.1±0.9	−2.4±1.0	−0.9±0.6	−1.9±0.8	−2.0±5.3
Song et al. (20)	−3.1±1.2	1.6±1.7	−3.3±0.9	–	−6.0±1.8
Wandel et al. (12)	−5.4±1.8	−5.6±2.2	−3.2±1.3	−6.0±2.1	–
Fredman et al. (11)	0.0±0.9	1.0±1.4	1.0±1.1	0.0±1.4	1.0±16.6
Ræder et al. (23)	−1.1±0.1	−1.3±0.1	–	−1.3±0.1	5.0±1.9
Pooled data					
Mean	−1.2±0.1	−1.4±0.1	−1.5±0.2	−1.5±0.1	−0.7±0.8
Confidence interval	−1.3 to −1.1	−1.5 to −1.3	−2.0 to −1.1	−1.6 to −1.4	−2.1 to 0.8

Number of subjects in sevoflurane/propofol groups on Table 2. Differences in time are the mean sevoflurane time minus the mean propofol time. Differences are reported as mean±pooled variance. −: data not collected.

Discussion

The results of this meta-analysis indicate that, in the elective surgical patient population, clear statistical differences exist between recovery from sevoflurane and isoflurane or propofol anaesthesia. In patients anaesthetized with sevoflurane, emergence from anaesthesia, response to commands and orientation occurred an average of 3–4 min earlier than in patients anaesthetized with isoflurane and at least 1 min earlier than in patients anaesthetized with propofol. The differences in the times to extubation averaged 1.5 min faster with sevoflurane than with either isoflurane or propofol.

The inability of meta-analysis to demonstrate an earlier time to recovery room discharge with the insoluble anaesthetic, sevoflurane, compared to isoflurane is consistent with published reports where the insoluble anaesthetic, desflurane, was compared to isoflurane (24–26) and propofol (25, 27–29). These data are perhaps counterintuitive to the expected benefit of a fast washout of an insoluble volatile anaesthetic. Possible explanations have been advanced for the failure of the new anaesthetic gases with low blood solubilities to result in earlier discharge times in shorter surgical procedures (27, 30). These include residual effects of adjuvant drugs such as opioids and sedatives employed during the perioperative period, and minimal stay requirements or practices imposed by recovery room personnel. In addition, in the case of sevoflurane, the similar tissue solubility to isoflurane could conceivably contribute to a delayed discharge in longer procedures.

An important outcome of this analysis was the demonstration of a statistically significant earlier time to the first analgesic in patients recovering from sevoflurane when compared to isoflurane. Although the analgesic potency of these volatile anaesthetics is at best weak, it seems that the more rapid washout of sevoflurane mandates an earlier attention to analgesic needs.

Meta-analysis has been employed by Dexter and Tinker to evaluate differences in recovery endpoints following desflurane and isoflurane anaesthesia (27). They noted a mean difference of 4.4 min for time to following commands. This difference is greater (i.e., faster) than the 3.0 min difference between sevoflurane and isoflurane for the same endpoint in the present analysis, and probably reflects the effects of the lower solubility of desflurane compared with sevoflurane (31). In addition, they were unable to demonstrate a benefit of desflurane over propofol in recovery endpoints in their meta-analysis. Dexter and Tinker stated that although meta-analysis could show statistically significant differences, there were only minor clinical differences between desflurane and isoflurane (27). A similar statement could be made in the present analysis although some would argue that any improvement in the time to return to consciousness following general anaesthesia reduces the incidence of earlier respiratory problems (32) and reduces the work load in the early recovery phase.

A limitation of the published studies used in this meta-analysis, as with other protocol-driven studies of recovery from anaesthesia, was the requirement to end anaesthesia in an abrupt fashion. These studies mandated that the anaesthetic not be discontinued or diminished until the last surgical stitch was in place. This prevented the clinician from slowly titrating off the anaesthetic at the end of the surgical repair, as is common in clinical practice. It could be predicted that all emergence times would be of shorter duration if titration were allowed, and it is unknown how early (or late) recovery endpoints would differ between anaesthetics if this were the case. We also speculate that the anesthesiologist might postpone tracheal extubation because the lack of pungency of sevoflurane (33, 34) makes it non-irritating to the airway. This might account for the smaller difference between sevoflurane and isoflurane in time to extubation as compared to time to emergence or orientation.

There also are issues regarding the validity of meta-analysis as a statistical technique in clinical medicine. Meta-analysis is typically employed to determine whether a true difference exists between treatments when outcomes are at variance. With one exception, in all published studies comparing sevoflurane to either isoflurane or propofol, sevoflurane was shown to improve early recovery endpoints. Moreover, meta-analysis is applied only to studies that have been published. There is an inherent risk that negative studies fail to be submitted or accepted for publication. Another limitation of meta-analysis is that it cannot identify specific factors which affected recovery outcomes (e.g., age, case duration, etc.); such an analysis requires individual patient data and specified factor analysis (e.g., analysis of variance). D'Agostino and Weintraub (14) and Goodman (35) have clearly stated that employing meta-analysis as a method of determining the clinical significance of a number of underpowered, suboptimally performed studies, cannot take the place of a well-designed, controlled study. We believe the chosen studies were not 'suboptimal', that is, the designs and controls were acceptable based on our selection criteria.

In summary, times to anaesthesia recovery endpoints, excluding recovery room discharge, in adult patients were significantly different (shorter) in patients receiving sevoflurane anaesthesia than isoflurane or propofol anaesthesia. Although meta-analysis of published randomized trials may have problems in application to medicine, including anaesthesia (35), this technique appears useful in indicating statistically significant drug effects in patient recovery from anaesthesia. The translation of statistically significant differences to clinically significant effects is always difficult and we leave this to the practitioners and their interpretation of these data.

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