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REPORTS OF ORIGINAL INVESTIGATIONS

Meta-analysis of desflurane and propofol average times and variability in times to extubation and following commands

Méta-analyse des temps moyens du desflurane et du propofol et de leur variabilité au niveau des temps jusqu'à l'extubation et la réponse à un ordre

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Abstract

Purpose *We performed a meta-analysis to compare the operating room recovery time of desflurane with that of propofol.*

Methods *Studies were included in which a) humans were assigned randomly to propofol or desflurane groups without other differences between groups (e.g., induction drugs) and b) mean and standard deviation were reported for extubation time and/or time to follow commands. Since there was heterogeneity of variance between treatment groups in the log-scale (i.e., unequal coefficients of variation of observations in the time scale), generalized pivotal methods for the lognormal distribution were used as inputs of the random effects meta-analyses.*

Results *Desflurane reduced the variability (i.e., standard deviation) in time to extubation by 26% relative to propofol (95% confidence interval [CI], 6% to 42%; $P = 0.006$) and reduced the variability in time to follow commands by 39% (95% CI, 25% to 51%; $P < 0.001$). Desflurane reduced the mean time to extubation by 21% (95% CI, 9% to 32%; $P = 0.001$) and reduced the mean time to follow commands by 23% (95% CI, 16% to 30%; $P < 0.001$).*

Conclusions *The mean reduction in operating room recovery time for desflurane relative to propofol was comparable with that shown previously for desflurane relative to sevoflurane. The reduction in variability exceeded that of sevoflurane. Facilities can use the percentage differences when making evidence-based pharmacoeconomic decisions.*

Résumé

Objectif *Nous avons réalisé une méta-analyse afin de comparer le temps de récupération en salle d'opération après une administration de desflurane par rapport au propofol.*

Méthode *Les études dans lesquelles a) des patients ont été randomisés en groupes recevant du propofol ou du desflurane sans autre différence entre les groupes (par ex. médicaments d'induction) et b) la moyenne et l'écart type étaient rapportés pour le temps jusqu'à extubation et/ou le temps nécessaire à la réponse à un ordre, ont été retenues. En raison de l'hétérogénéité du point de vue de la variance entre les groupes de traitement sur une échelle logarithmique (c.-à-d. des coefficients inégaux de variation des observations dans l'échelle de temps), des méthodes pivot généralisées pour la distribution log-normale ont été utilisées pour saisir les méta-analyses d'effets aléatoires.*

Résultats *Le desflurane a réduit la variabilité (c.-à-d. l'écart type) en matière de temps jusqu'à extubation de 26 % par rapport au propofol (intervalle de confiance [IC] 95 %, 6 % à 42 %; $P = 0{,}006$) et a réduit la variabilité en matière de temps jusqu'à la réponse à un ordre de 39 %*

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(IC 95 %, 25 % à 51 %; P < 0,001). Le desflurane a réduit le temps moyen jusqu'à extubation de 21 % (IC 95 %, 9 % à 32 %; P = 0,001) et réduit le temps moyen jusqu'à la réponse à un ordre de 23 % (IC 95 %, 16 % à 30 %; P < 0,001).

Conclusion *La réduction moyenne du temps de récupération en salle d'opération lors de l'administration de desflurane par rapport à du propofol était comparable à celle précédemment démontrée lors de la comparaison du desflurane au sévoflurane. La réduction de la variabilité a dépassé celle du sévoflurane. Les établissements peuvent utiliser les différences de pourcentage pour prendre des décisions pharmaco-économiques fondées sur des données probantes.*

Many hospitals strive to reduce their non-operative operating room (OR) time, i.e., time in the OR when surgery is not being performed. Reducing non-operative time can reduce labour costs for ORs with more than eight hours of cases.[1-5]

Many surgeons focus on non-operative time. Vitez and Macario asked surgeons to score the importance of particular attributes of anesthesia groups using a scale from 0 to 4; 0 = "no importance", and 4 = "a factor that would make me switch groups/hospitals".[6] The mean score was 4.0 for "ability to calmly manage a crisis". The mean score was only slightly less (3.9) for "patient quick to awaken", demonstrating the importance surgeons place on promptly beginning the next case.

We previously used data from an anesthesia information management system to model the time from end of surgery to tracheal extubation.[7] We applied that knowledge to perform meta-analyses of trials comparing extubation times following maintenance with desflurane and sevoflurane.[7] Desflurane reduced the mean extubation time relative to sevoflurane by 25% and reduced the standard deviation by 21%.[7] Desflurane reduced the mean extubation time relative to isoflurane by 34% and reduced the standard deviation by 36%.[8]

In our earlier analyses, we assumed that the coefficient of variation does not vary according to treatment, i.e., type of anesthetic. The assumption held for desflurane *vs* sevoflurane (see the Results section 2 and Fig. 5 of reference 7). However, we illustrate in the Appendix that the assumption does not hold true for desflurane *vs* propofol. We modified the statistical analysis by using generalized pivotal methods to account for differences in the coefficient of variation between groups. To explain the method, we use data from a small observational study of the times required to prepare propofol for the next case. In this article, we applied generalized pivotal methods to compare OR recovery times between desflurane and propofol.[9-34]

Methods

To identify published manuscripts comparing OR recovery times after desflurane and propofol in humans, we searched PubMed on January 10, 2011 using the following criteria: desflurane AND (propofol OR Diprivan) AND (extubation OR extubate OR command OR recover OR recovery OR cost), limited to humans. The search yielded 168 articles. A search of Web of Knowledge without limits yielded 424 articles, and a search of the Cochrane Library yielded no additional articles. One author (R.E.W.) read the titles and abstracts of the articles and identified 82 articles that potentially satisfied our inclusion criteria: a) humans assigned randomly to desflurane or propofol groups without other differences between groups, e.g., induction drugs; b) mean and standard deviation reported for extubation time and/or time to follow commands; and c) peer-reviewed publication, i.e., exclusion of letters, editorials, and meeting abstracts. No restrictions were placed on date or language. The references of the articles were also searched in an attempt to identify additional articles, and none were found. Two OR endpoints were included because recovery times can be sensitive to the selection of the endpoint.[7,8,35] Two authors (R.E.W., F.D.) independently reviewed the 82 articles and independently abstracted data from the 26 articles meeting the inclusion criteria, including covariates and measures of study quality (Table 1).[36] Overall, 56 articles were excluded: 20 because neither endpoint was reported; 13 because the articles did not contain original data; 13 because the two groups were not matched (e.g., the desflurane group received nitrous oxide but the propofol group did not);[A] seven because the articles did not report standard deviations or standard errors; and three because patients had not been randomized. There were two discrepancies in data extraction involving two of the remaining 26 articles. One discrepancy was an error by R.E.W. caught by F.D., and the other was an error by F.D. caught by R.E.W. For the first error, a weighted average was copied incorrectly from the preceding row, and for the second error, the author judged incorrectly that a target-controlled infusion had been used.

Percentage reductions in mean time and 95% confidence interval (CI) were calculated as described in the Appendix using Microsoft® Excel, Visual Basic for Applications.[37] Percentage reductions in standard deviation and confidence

[A] One article was unclear about whether the desflurane and propofol groups had both received nitrous oxide. An e-mail to the author clarified the protocol.

Table 1 Characteristics of studies listed in sequence of increasing observed effect of desflurane *vs* propofol

Reference	*n* Subjects Propofol	*n* Subjects Desflurane	Sequence Generation	Remifentanil	Target Infusion	Titrated BIS or AEP	LMAD	Year	Mean Age (yr)	Mean Weight (kg)	Mean Duration (min)
7	30	30				Yes		2007	43	60	99
10	30	30	Yes		Yes			2009	56	72	91
11	20	20	Yes	Yes				2007	26	67	82
12	23	22						1992	34	75	49
13	25	25		Yes				2001	48	75	141
14	32	31		Yes	Yes			2001	18	59	75
15	40	40		Yes		Yes		2003	46	66	96
16	15	15						1991	37	74	31
17	13	15						1993	34	64	20
18	25	25	Yes	Yes		Yes	Yes	2006	42	79	51
19	35	35		Yes	Yes			2001	40	76	67
15	40	40		Yes				2003	48	69	91
20	30	30					Yes	1998	44	65	25
21	23	23						1991	30	64	62
22	50	54	Yes					2002	35	66	32
23	14	16						1993	28	78	91
24	30	30	Yes			Yes	Yes	2002	75	74	48
25	14	14						1997	77	67	201
26	20	20		Yes				1998	36	67	63
27	35	40	Yes			Yes	Yes	2001	55	68	38
28	17	17	Yes			Yes		2001	30	70	79
29	29	31	Yes					1998	27	66	68
30	40	40	Yes					1998	29	71	71
31	18	18		Yes	Yes			2004	50	76	342
32	20	20						1996	24	79	
33	11	12				Yes		2000	40	125	170
34	100	100						2007	52	72	67

n = sample size; LMAD = laryngeal mask airway device with all tracheal intubations with an endotracheal tube. Sequence Generation means that the patients were randomized to groups using either a random number table or a computer random number generator. Sequence allocation concealment (e.g., opaque envelopes) is not listed because it was reported only in one study.[9] Remifentanil is use of remifentanil infusion for intraoperative analgesia. Target Infusion refers to computer-controlled infusion to deliver predicted constant plasma concentration or pre-specified declining dose per minute, uninfluenced by observed hemodynamics. Titrated BIS or AEP refers to dose adjustment to maintain bispectral index or auditory evoked potentials[9] at pre-specified levels. Mean Duration refers to the duration of anesthesia or duration of surgery when duration of anesthesia was unavailable. Reference [15] appears twice because the article included studies with and without BIS

interval were also calculated. The correlation between these two summary measures was studied, and the covariates were explored using Kendall's rank correlation coefficient. Meta-regression was not used because the covariates that we expected to influence results (e.g., obese patients undergoing longer anesthetics would have larger differences) were not binary study characteristics but were measured variables with sampling error. The P values are two-sided and exact (StatXact® 9, Cytel Software Corporation, Cambridge, MA, USA). Fail-safe calculations assessed whether publication bias could have influenced conclusions.[38]

Economic interpretation of the meta-analysis results depends on the influence of time of emergence from general anesthesia on OR time. The Institutional Review Board at the University of Iowa approved observation of anesthesia providers at the ambulatory surgery centre. The times to prepare propofol for use in infusion syringe pumps were recorded by timing anesthesia providers as they drew up 50 mL of propofol and purged air from the attached

extension tubing. Observational details and analyses of preparation times are described in the Appendix. In addition, activities of OR staff, including nurses, were observed from the time of end of surgery to tracheal extubation.

Results

There were few substantive differences in quality among the studies. None of the studies were blinded for desflurane

Table 2 Times from end of surgery to extubation and from end of surgery to follow commands for each study in Table 1

Reference	Propofol (min) Mean (SD)		Desflurane (min) Mean (SD)		Desflurane Reduction in Mean		Desflurane Reduction in SD	
	Extubation	Commands	Extubation	Commands	Extubation	Commands	Extubation	Commands
7	8.2 (3.0)		13.7 (5.0)		−68%		−67%	
10	6.4 (4.2)	8.0 (0.8)	7.6 (0.7)	9.2 (0.7)	−14%	−15%	84%	14%
11	6.8 (3.7)	7.8 (3.7)	7.3 (3.4)	8.7 (3.3)	−8%	−12%	9%	11%
12		10.6 (6.3)		11.0 (5.5)		−4%		13%
13	5.5 (3.3)		5.7 (2.5)		−3%		25%	
14	10.4 (3.0)		10.2 (5.1)		0%		−71%	
15	6.8 (4.6)		6.5 (4.1)		5%		11%	
16		10.0 (4.8)		9.4 (4.4)		4%		9%
17		5.3 (2.3)		5.0 (0.9)		6%		62%
18	6.9 (2.6)	6.6 (2.8)	6.4 (2.6)	6.0 (2.2)	6%	9%	0%	22%
19	6.3 (2.1)	8.7 (2.9)	5.3 (2.5)	7.3 (1.9)	15%	16%	−20%	35%
15	10.5 (5.9)		8.3 (6.1)		21%		−4%	
20	5.6 (2.9)	6.6 (3.0)	4.4 (1.5)	5.1 (1.5)	22%	23%	49%	50%
21		8.3 (3.9)		6.4 (2.4)		23%		39%
22		4.6 (2.2)		3.5 (1.8)		23%		18%
23		12.2 (15.5)		9.1 (3.1)		26%		83%
24	8.7 (3.8)	10.5 (3.9)	6.1 (3.1)	7.7 (3.0)	29%	26%	18%	23%
25	9.9 (6.5)	14.3 (8.0)	6.9 (3.0)	7.4 (3.2)	32%	48%	55%	61%
26	9.8 (4.0)	10.6 (4.5)	6.7 (2.8)	7.2 (2.8)	31%	32%	30%	38%
27		6.0 (2.0)		4.0 (2.0)		32%		0%
28		8.0 (4.0)		5.0 (4.0)		35%		−3%
29		7.0 (6.0)		4.0 (2.0)		42%		67%
30	8.9 (5.3)	8.3 (6.9)	5.1 (3.3)	4.7 (2.6)	41%	42%	38%	63%
31	13.2 (2.3)		7.5 (1.3)		43%		43%	
32		15.1 (1.8)		6.4 (0.4)		58%		78%
33	13.2 (7.6)		5.6 (1.4)		58%		82%	
34	6.2 (3.2)		2.3 (1.6)		64%		49%	

SD = standard deviation. Reduction in Mean refers to the reduction in the lognormal mean of time to extubation or time to follow commands, calculated using pivotal methods. Negative reductions indicate that values were larger in the desflurane group compared with the propofol group (see Appendix equations (1) and (10)). The corresponding standard errors of the estimates are not reported because they are in the log-scale. Reduction in SD refers to the reduction in the standard deviation of the time to extubation or time to follow commands, also calculated using pivotal methods (see Appendix equations (16) and (17)). The inverses of these standard errors are proportional to the areas of the circles in the Figure

Table 3 Desflurane reductions in operating room recovery times relative to propofol

	All Studies	Excluding the studies with the largest and smallest reductions
Mean time to extubation	21% (95% CI, 4% to 36%; $P = 0.010$)	21% (95% CI, 9% to 32%; $P = 0.001$)
Mean time to follow commands	25% (95% CI, 5% to 41%; $P = 0.008$)	23% (95% CI, 16% to 30%; $P < 0.001$)
Standard deviation of time to extubation	30% (95% CI, 6% to 48%; $P = 0.008$)	26% (95% CI, 6% to 42%; $P = 0.005$)
Standard deviation of time to follow commands	40% (95% CI, 26% to 52%; $P < 0.001$)	39% (95% CI, 25% to 51%; $P < 0.001$)

Results are reported as mean with 95% confidence interval (CI). Fail-safe analyses showed that single additional studies with 0% difference would require > 3,000 patients per group for a resulting $P > 0.05$[38]

vs propofol, and all studies were randomized. All patients received the drugs to which they were randomized (Table 1). Nine of the 26 studies reported randomization using either a random number table or a computer random number generator.

Desflurane reduced the variability (standard deviation) in time to extubation by approximately 26% relative to propofol, the variability in time to follow commands by 39%, the mean time to extubation by approximately 21%, and the mean time to follow commands by 23% (Tables 2-3, Figure). Heterogeneity among studies for each endpoint ($P < 0.001$) was unexplained by other measured variables (Table 4).

We observed seven cases in which a propofol anesthetic was used. In all cases, at least one OR nurse or surgical technologist was performing no discernable activity for at least 100 sec prior to tracheal extubation (95% CI > 66% of cases). The time to draw up propofol and set up an infusion pump averaged one minute (see Appendix).

Discussion

Desflurane proportionally reduces the mean time to extubation and time to follow commands relative to propofol (21% and 23%), approximately the same as sevoflurane (25% and 19%)[7] but less than isoflurane (34% and 34%).[8] Clinicians provide anesthesia care in heterogeneous ways (Table 1) and meta-analysis of economic endpoints provides managerial insight into overall (pooled) effect (Table 3).[39] The principal limitation is that since drug (treatment) effect is proportional,[7] for results to be useful economically to a facility, results need to be converted to absolute reductions in time using the facility's patients' typical OR recovery times. For example, a 20% reduction in the mean time represents 1.5 min for patients with the brief mean interval of 7.5 min *vs* 2.5 min for patients with the long mean interval of 12.5 min.[7] Differences between anesthetic agents in OR recovery times are studied since they can limit OR throughput, based on non-anesthesia OR personnel waiting for the patient to be extubated during emergence for most (> 66%) cases. Outside of ORs there typically are additional personnel (e.g., housekeepers and post-anesthesia care unit nurses) waiting for the end of cases, since surgical suites appropriately staff for multiple ORs in which cases end simultaneously.[40,41] Additional personnel (e.g., housekeepers and postanesthesia care unit nurses) are typically outside of ORs waiting for cases to end, since surgical suites are appropriately staffed for multiple ORs on the basis of cases that end simultaneously.[40,41]

Achievable reductions in direct OR costs resulting from time savings in the OR can be calculated as described in the Discussion of reference 7. Specific values are unique to each facility (e.g., application of our results depends on the number of ORs with more than eight hours of cases daily). Other endpoints, such as time to home discharge

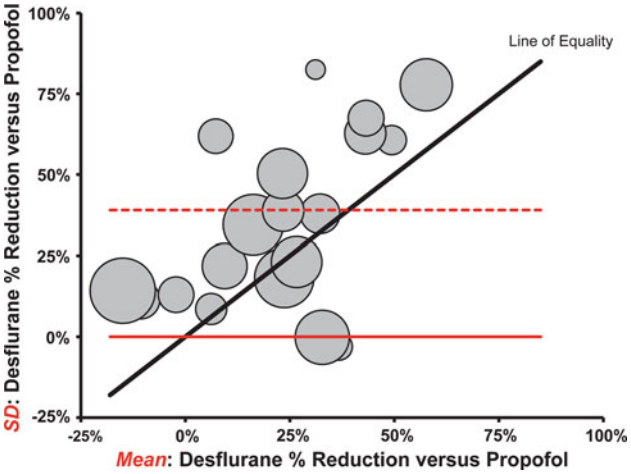

Figure Reduction in variability in time to follow commands with desflurane instead of propofol. The value along the vertical axis is the reduction in the standard deviation of the time to follow commands by using desflurane instead of propofol, calculated using equations (11) to (17). The dotted horizontal red line at 39% is the weighted mean estimate reported in the Results and the right-hand column of Table 3. The solid horizontal red line shows 0% increase. Each circle shows the point estimates of the reductions in variability from a study as reported in Table 2. However, the relationship in Table 2 is less apparent because the table is sorted in ascending sequence of the percentage reduction in the mean time to extubation. The fact that 17 of the 19 studies are displayed above the solid horizontal 0% line highlights that the studies showed significant reductions in the variability of time to follow commands. The area of each circle is proportional to the precision of that estimate (i.e., 1 divided by the square of the standard error of the proportional reduction in standard deviation). Studies with greater precision appear as larger circles. As described below equation (10), the standard error is calculated by dividing the width of the 75% confidence interval by the corresponding inverse of the standard normal distribution. This graph is novel because previous studies did not estimate the standard error of the reduction in variability for each study in which desflurane was compared with sevoflurane and isoflurane. We previously estimated the standard error based on a pooled quantity from secondary observations of extubation times (see Appendix of reference 7). The graph is also novel because none of the prior studies reported a significant reduction in the standard deviation because the statistical methodology described in this article had not previously been developed. The Figure also shows the estimated reduction in the mean time to follow commands by using desflurane instead of propofol, plotted along the horizontal axis. The standard error of that estimate is not shown, as the focus of the plot is the reduction in variability along the vertical axis. The methodologically important finding of the Figure is highlighted by the line of equality. For several studies, the percentage reductions in the variability in the time to follow commands exceeded the reductions in the mean time to follow commands. Thus, there are unequal coefficients of variation between treatment groups, which differs from Fig. 5 of reference 7 for time to extubation with desflurane *vs* sevoflurane. For statistical details, see the Appendix after equation (9)

Table 4 Association between independent variables in Tables 1 and 2 and percentage reductions with desflurane (Table 2)

	Mean Extubation		Mean Commands		SD Extubation		SD Commands	
	Kendall's Correlation	Uncorrected *P* value	Kendall's Correlation	Uncorrected *P* value	Kendall's Correlation	Uncorrected *P* value	Kendall's Correlation	Uncorrected *P* value
Variables of Table 1 from left to right								
Total sample size	−0.07	0.74	0.02	0.92	−0.25	0.18	−0.06	0.75
Sequence generation	−0.18	0.44	0.03	0.90	0.04	0.88	−0.32	0.11
Remifentanil	−0.24	0.28	−0.24	0.26	−0.48	0.02	−0.14	0.53
Target infusion	−0.14	0.55	−0.31	0.14	−0.07	0.78	−0.10	0.66
Titrated BIS or AEP	−0.09	0.72	0.12	0.60	−0.16	0.51	−0.39	0.05
LMAD	0.03	0.95	−0.02	0.96	−0.03	0.95	−0.16	0.47
Year	−0.34	0.07	−0.18	0.33	−0.15	0.44	−0.33	0.06
Mean age (yr)	0.12	0.54	−0.13	0.45	0.34	0.06	−0.24	0.16
Mean weight (kg)	0.25	0.18	0.03	0.89	0.21	0.27	−0.03	0.89
Mean duration (min)	−0.06	0.78	0.22	0.23	0.13	0.49	0.14	0.45
Variable of Table 2 columns 2 and 3								
Propofol value (min)	0.30	0.11	0.21	0.24	0.30	0.10	0.20	0.25

Variables from Table 1 - see Table 1 for definitions. Propofol value (min) - on the far left, it refers to the mean time to extubation for propofol, and on the far right, it refers to the standard deviation of the time to follow commands. To interpret the sign of Kendall's rank correlation coefficient for the binary variables (e.g., use of remifentanil), absence was coded as 0 and presence as 1. Given 40 comparisons, Bonferroni correction of $P = 0.05$ would treat $P \leq 0.001$ as statistically significant. SD = standard deviation. BIS = bispectral index; AEP = auditory evoked potentials; LMAD = laryngeal mask airway device

and nausea, have previously undergone meta-analysis[42-44] and are also of value when comparing the overall impact of the selection of anesthetic drugs. Selection of propofol adds approximately one minute to fill a syringe for infusion and to set up the infusion pump (see Appendix).

The novel findings of our study are twofold. First, as shown in the Figure, the reductions in the variabilities in OR recovery time are larger when desflurane is compared with propofol (26%, time to extubation and 39%, time to follow commands) than when desflurane is compared with sevoflurane (21% and 22%, respectively).[7] Second, as is the focus of the Appendix, the reductions in the variabilities relative to propofol (26% and 39%) are larger than the corresponding mean reductions (21% and 23%). Such results are striking when considered in light of the traditional weighted mean difference meta-analysis that assumes a 0% reduction in variability. The pharmacokinetic/dynamic basis for the difference between reductions in standard deviation and mean is unknown. Variability matters clinically, as it contributes to the incidence of prolonged extubation times (e.g., > 15 min). Anesthesiologists rate recovery from propofol as poor when such prolonged extubations occur.[45] Resulting intangible OR costs include significantly longer times to incision of to-follow cases[7] (e.g., from surgeons leaving surgical suite[46]). The methods described in the Appendix and summarized in the Figure can be used in future clinical trials and meta-analyses of such trials with the reduction in variability of task duration as a primary study endpoint.

In conclusion, the mean reduction in OR recovery times for desflurane relative to propofol was comparable with that shown previously for desflurane relative to sevoflurane. The reduction in variability with propofol exceeded that compared with sevoflurane. Facilities can use the percentage differences when making evidence-based pharmacoeconomic decisions.

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Appendix

Observational study

The raw data are observations of task durations x_{ijp}; for treatments $i = 1, 2$; studies $j = 1, \ldots, g$; and patients $p = 1, \ldots, n_{ij}$.

We start with a one-sample situation (i.e., $i = 1$ and $j = 1$): times observed to draw up 50 mL of propofol from a 50 mL vial into a 60 mL syringe using a spike dispensing device. There were $n_{11} =$ a total of 14 observations from ten anesthesia providers. Times in seconds were:

16, 17, 20, 21, 21, 27, 29, 33, 36, 42, 52, 55, 56, 70

The sample mean $\bar{x}_{11} = 35.4$ sec and the sample standard deviation $s_{11} = 17.1$ sec These estimates are similar to the mean (standard deviation) 35 (5) sec that anesthesia providers took to prepare a 10 mL syringe of saline,[47] the 28 (10) sec that nurses took to prepare an injection of meperidine,[48] and the 47 (16) sec that nurses took to insert a syringe and program a patient-controlled analgesia pump.[48] The mean of the natural logarithms $\hat{\mu}_{11} = 3.46$ and standard deviation $\hat{\sigma}_{11} = 0.48$. These are sample estimates of the lognormal distribution's mean μ and standard deviation σ in the log-scale.

The generalized pivotal confidence interval (CI) for the mean was calculated by performing the following $m = 100{,}000$ computer simulations:[49]

For $k = 1$ to m

Generated Z^k: a normally distributed random number with mean 0 and variance 1

Generated U^k: the square root of a chi-square distributed random number with $n_{ij} - 1$ degrees of freedom

$$\text{Set } T_{ij}^k = \hat{\mu}_{ij} - \frac{Z^k}{\sqrt{n_{ij}}}\left(\frac{\hat{\sigma}_{ij}}{U^k/\sqrt{n_{ij}-1}}\right) + \frac{1}{2}\left(\frac{\hat{\sigma}_{ij}}{U^k/\sqrt{n_{ij}-1}}\right)^2 \quad (1)$$

Next k

Calculated the $100(\alpha/2)$ and $100(1 - \alpha/2)$ percentiles of the simulated. $\exp\left(T_{ij}^k\right)$.

For example, using the above $n_{11} = 14, \hat{\mu}_{11} = 3.46$, and $\hat{\sigma}_{11} = 0.48$, the calculated 95% CI is 28 to 51 sec. Equation (1) for T_{ij}^k follows from the two statistical properties that are used in Student's t test:[50] $\sqrt{n_{ij}}\left(\hat{\mu}_{ij} - \mu_{ij}\right)/\sigma_{ij}$ follows a normal distribution (Z) and $\left(n_{ij} - 1\right)\hat{\sigma}_{ij}^2/\sigma_{ij}^2$ follows a chi-square distribution (U^2). The resulting CI is exact.[49]

The other example with one treatment group is the time to set up the infusion pump using the patient's weight from the anesthetic record. Times to bring the pump into the OR and to program it to administer propofol were excluded as these tasks were performed before the start of the first case, as in the initial checking and filling of the desflurane vaporizer. The $n_{12} = 13$ observations had $\bar{x}_{12} =$ 26.4 sec, $s_{12} = 13.8$ sec, $\hat{\mu}_{12} = 3.14$, and $\hat{\sigma}_{12} = 0.54$. Performing the simulations of equation (1), the 95% CI is 20 to 42 sec. We suspect these times are much briefer than the 8-13 min required for setting up other infusion pumps,[48-53] because our providers used pre-programmed pumps.

Meta-analysis

The meta-analyses have data with treatments $i = 1, 2$ and studies $j = 1, \ldots, g$, where $g = 17$ for time to extubation and $g = 19$ for time to follow commands. Letting $i = 1$ refer to propofol and $i = 2$ refer to desflurane, the n_{1j} are in Table 1 column 2 and the n_{2j} are in column 3. The $\bar{x}_{1j}$, s_{1j}, $\bar{x}_{2j}$, and s_{2j} are in Table 2 columns 2 through 5, respectively. For example, from the first rows of Tables 1 and 2, $n_{12} = 30$, $\bar{x}_{12} = 13.7$ min, and $s_{12} = 5.0$ min.

The method of moments was used to convert the times from Table 2 into the log-scale. For lognormal random variables, the expected value

$$E\left(x_{ijp}\right) = \exp\left(\mu_{ij} + \frac{1}{2}\sigma_{ij}^2\right) \quad (2)$$

and variance

$$Var\left(x_{ijp}\right) = \left(\exp\left[\sigma_{ij}^2\right] - 1\right)\exp\left(2\mu_{ij} + \sigma_{ij}^2\right). \quad (3)$$

Substituting unbiased sample estimates for population characteristics:

$$\bar{x}_{ij} \cong \exp\left(\hat{\mu}_{ij} + \frac{1}{2}\hat{\sigma}_{ij}^2\right) \quad (4)$$

and

$$s_{ij}^2 \cong \left(\exp\left[\hat{\sigma}_{ij}^2\right] - 1\right)\exp\left(2\left[\hat{\mu}_{ij} + \frac{1}{2}\hat{\sigma}_{ij}^2\right]\right). \quad (5)$$

Substituting equation (4) into equation (5) and rearranging terms leads to the solutions:

$$\hat{\mu}_{ij} = \ln\left(\bar{x}_{ij}\right) - \frac{1}{2}\ln\left(\frac{s_{ij}^2}{\bar{x}_{ij}^2} + 1\right) \quad (6)$$

and

$$\hat{\sigma}_{ij}^2 = \ln\left(\frac{s_{ij}^2}{\bar{x}_{ij}^2} + 1\right). \quad (7)$$

For example, from the first row of Table 2, the reported $\bar{x}_{12} = 13.7$ min and $s_{12} = 5.0$ min. Substituting these

values into equations (6) and (7) gives $\hat{\mu}_{12} = 2.55$ and $\hat{\sigma}_{12} = 0.35$.

A feature of the lognormal distribution is that the coefficient of variation depends only on the variance in the log-scale:

$$CV_{ij} = \sqrt{-1 + \exp\left(\sigma_{ij}^2\right)}. \tag{8}$$

The method developed previously for meta-analysis of desflurane *vs* sevoflurane was based on a common coefficient of variation between treatments (i.e., common variance in the log-scale).[7] We performed the following $m = 100{,}000$ simulations to test for equality of the coefficient of variation between treatments:[54]

For $k = 1$ to m

Generated U_1^k: the square root of a Chi square distributed random number with $n_{1j} - 1$ degrees of freedom

Generated U_2^k: the square root of a Chi square distributed random number with $n_{2j} - 1$ degrees of freedom

$$\text{Set } T_{CV}^k = \sqrt{-1 + \exp\left(\left[\frac{\hat{\sigma}_{1j}}{U_1^k/\sqrt{n_{1j}-1}}\right]^2\right)} - \sqrt{-1 + \exp\left(\left[\frac{\hat{\sigma}_{2j}}{U_2^k/\sqrt{n_{2j}-1}}\right]^2\right)} \tag{9}$$

Next k

Calculated the proportion of the m simulations for which the $T_{CV}^k > 0$.

Since only the sign of T_{CV}^k was used, equation (9) was programmed by comparing $(n_{1j}-1)\hat{\sigma}_{1j}^2 \big/ \left(U_1^k\right)^2$ and $(n_{2j}-1)\hat{\sigma}_{2j}^2 \big/ \left(U_2^k\right)^2$. If one is larger than the other for fewer than 0.025 m or more than 0.975 m simulations, then there is a statistically significant difference in the variance in the log-scale at $\alpha = 0.05$ and thus in the coefficients of variation. Typical tests for the equality of variance in the log-scale (e.g., Bartlett's test or Levene's test) could not be used because raw data were not available, just the parameters obtained from equation (7).

Equality of the coefficient of variation between treatment groups (i.e., desflurane and propofol) was rejected at $P < 0.05$ for approximately one-third of the studies, five of 17 studies of time to extubation and seven of 19 studies of time to follow commands. In comparison, equality was rejected at $P < 0.10$ for only three of 29 studies comparing time to extubation between sevoflurane and desflurane (see Results section 2 of reference 7). The inequality was also apparent from the pooled (meta-analysis) results. Desflurane reduced the mean and standard deviation of time to follow commands by 23% and 37%, respectively, relative to propofol (i.e., an absolute difference of 14%) (Table 3). If the coefficient of variation had been unchanged by treatment, these estimates of the reductions would not have differed significantly. Sevoflurane's reductions[7] were 19% and 22%, respectively, (within 3% of one another) and isoflurane's reductions[8] were 34% and 31%, respectively (also within 3% of one another). The Figure shows the inequality of percentage reductions for the 19 studies of time to follow commands. We used generalized pivotal methods because they do not assume a common coefficient of variation between treatments, in contrast to both of the two previously published methods for meta-analyses of ratios.[7,37,55]

Pooling lognormal distributions among studies relies on ratios of the lognormal means:[7]

$$\delta_j = \log\frac{E(x_{2jp})}{E(x_{1jp})} = \mu_{2j} + \frac{1}{2}\sigma_{2j}^2 - \left(\mu_{1j} + \frac{1}{2}\sigma_{1j}^2\right).$$

The generalized pivotal statistic for δ_j is

$$T_{\hat{\delta}_j}^k = T_{2j}^k - T_{1j}^k. \tag{10}$$

For each of the j = 1, …, g studies, we calculated the mean $\hat{\delta}_j$ and variance V_j of the m simulated $T_{\hat{\delta}_j}$. When $n_{1j} \cong n_{2j}$, which was true for all studies (Table 1), the distribution of $T_{\hat{\delta}_j}$ is approximately symmetric. However, the right-hand term of equation (1) involves inverse chi-square distributions with occasional very large numbers for the studies with sample sizes < 20. Since some of $T_{\hat{\delta}_j}$ was symmetric with outliers, V_j was calculated by dividing the width of the 75% CI by the corresponding inverse of the standard normal distribution (2 × 0.67449).

The fixed-effects meta-analysis estimate

$$\hat{\delta}_{fixed} = \frac{\sum_{j=1}^{g}\left(\hat{\delta}_j \big/ V_j\right)}{\sum_{j=1}^{g}\left(1/V_j\right)}. \tag{11}$$

Applying the random-effects meta-analysis specification, the log-ratios δ_j vary among studies following $\delta_j \sim N(\delta, \tau^2)$, and $\hat{\delta}_j|\delta_j \sim N(\delta_j, V_j)$. From DerSimonian and Laird,[56]

$$\hat{\tau}_{DL}^2 = \max\left\{0, \frac{Q - (g-1)}{\sum_{j=1}^{j=g}\left(1/V_j\right) - \left[\sum_{j=1}^{j=g}\left(1/V_j^2\right)\right] \big/ \left[\sum_{j=1}^{j=g}\left(1/V_j\right)\right]}\right\}, \tag{12}$$

where the heterogeneity coefficient

$$Q = \sum_{j=1}^{j=g}\left(\hat{\delta}_j - \hat{\delta}_{fixed}\right)^2 \Big/ V_j. \tag{13}$$

The random-effect estimate of the treatment effect is

$$\hat{\delta}_{DL} = \frac{\sum_{j=1}^{j=g} \frac{\hat{\delta}_j}{V_j + \hat{\tau}^2_{DL}}}{\sum_{j=1}^{j=g} \frac{1}{V_j + \hat{\tau}^2_{DL}}}, \quad (14)$$

with variance

$$V(\hat{\delta}_{DL}) = \frac{1}{\sum_{j=1}^{j=g} \frac{1}{V_j + \hat{\tau}^2_{DL}}}. \quad (15)$$

The asymptotic 95% CI for δ is given by $\hat{\delta}_{DL} \pm 1.96\sqrt{V(\hat{\delta}_{DL})}$, where 1.96 is the inverse of the standard normal distribution. Equations (11-15) are no different from most meta-analyses and are shown to simplify the subsequent paragraphs.

The conditions of our sensitivity analysis of time to extubation (see Results) match the conditions of Sidik and Jonkman's Monte-Carlo simulations that compared the performance of DerSimonian and Laird's method to that of restricted maximum likelihood estimation for estimating τ.[57] Specifically, the $g = 17$ values of $\hat{\delta}_j$ were sorted in ascending sequence, and the smallest and largest values were trimmed (see Table 3). Since Table 2 is sorted in this sequence, it is the studies in the first and last rows that were excluded. The remaining 15 values and their variances were substituted into equations (11) and (12) giving $\hat{\tau}^2_{DL} = 0.061$. This condition of $g = 15$ and $\tau^2 < 0.1$ are in Sidik and Jonkman's[57] Tables 1 and 2. The bias and mean square error of estimates of τ^2 are ≤ 0.005 for both methods (i.e., an order of magnitude smaller than the observed $\hat{\tau}^2_{DL}$.).[56] Therefore, we used the simpler Dersimonian and Laird method.

Applying the $\hat{\tau}^2_{DL} = 0.061$ in equations (14) and (15), the pooled estimate $\hat{\delta}_{DL} = -0.236$, and its standard error $se(\hat{\delta}_{DL}) = \sqrt{V(\hat{\delta}_{DL})} = 0.073$. The approximate 95% CI for $\delta = \log [E(X_2)/E(X_1)]$ extends from -0.378 to -0.093, where $-0.378 = -0.236 - (1.96)(0.073)$ and $-0.093 = -0.236 + (1.96)(0.073)$. The corresponding estimate for the percentage reduction in time to extubation by the use of desflurane instead of propofol is given by $(E(X_1) - E(X_2))/E(X_1) = 1 - \exp\left(\hat{\delta}_{DL}\right) = 1 - \exp(-0.236) = 21\%$. The corresponding 95% CI extends from $1 - \exp(-0.093) = 9\%$ to $1 - \exp(-0.378) = 32\%$. See the top row of Table 3 for these values.

To estimate the relative reduction in variability, equation (1) is substituted into equation (3) to obtain the pivotal statistic for the variance in the time scale:[54]

$$T^k_{\sigma^2_{ij}} = \left(\exp\left[\left(\frac{\hat{\sigma}_{ij}}{U^k/\sqrt{n_{ij} - 1}} \right)^2 \right] - 1 \right) \exp\left(2T^k_{ij} \right). \quad (16)$$

Following equation (10), the generalized pivotal statistic for the logarithm of the ratios of the standard deviations[54] is

$$T^k_{\hat{\delta}^{\sigma}_j} = \frac{\ln\left(T^k_{\sigma^2_{2j}} \right) - \ln\left(T^k_{\sigma^2_{1j}} \right)}{2}. \quad (17)$$

The meta-analysis of equations (11) to (15) is then applied. Neither of the alternative statistical methods (Higgins[37] or Friedrich[55] can analyze the reduction in variances or differences in coefficients of variation (equation (9)).

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