

Impact of Anesthesia Management Characteristics on Severe Morbidity and Mortality

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Background: Quantitative estimates of how anesthesia management impacts perioperative morbidity and mortality are limited. The authors performed a study to identify risk factors related to anesthesia management for 24-h postoperative severe morbidity and mortality.

Methods: A case-control study was performed of all patients undergoing anesthesia (1995-1997). Cases were patients who either remained comatose or died during or within 24 h of undergoing anesthesia. Controls were patients who neither remained comatose nor died during or within 24 hours of undergoing anesthesia. Data were collected by means of a questionnaire, the anesthesia and recovery form. Odds ratios were calculated for risk factors, adjusted for confounders.

Results: The cohort comprised 869,483 patients; 807 cases and 883 controls were analyzed. The incidence of 24-h postoperative death was 8.8 (95% confidence interval, 8.2-9.5) per 10,000 anesthetics. The incidence of coma was 0.5 (95% confi-

dence interval, 0.3-0.6). Anesthesia management factors that were statistically significantly associated with a *decreased* risk were: equipment check with protocol and checklist (odds ratio, 0.64), documentation of the equipment check (odds ratio, 0.61), a directly available anesthesiologist (odds ratio, 0.46), no change of anesthesiologist during anesthesia (odds ratio, 0.44), presence of a full-time working anesthetic nurse (odds ratio, 0.41), two persons present at emergence (odds ratio, 0.69), reversal of anesthesia (for muscle relaxants and the combination of muscle relaxants and opiates; odds ratios, 0.10 and 0.29, respectively), and postoperative pain medication as opposed to no pain medication, particularly if administered epidurally or intramuscularly as opposed to intravenously.

Conclusions: Mortality after surgery is substantial and an association was established between perioperative coma and death and anesthesia management factors like intraoperative presence of anesthesia personnel, administration of drugs intraoperatively and postoperatively, and characteristics of delivered intraoperative and postoperative anesthetic care.

NOWADAYS, anesthesia is considered safe because few serious perioperative adverse outcomes such as coma or death are related directly to anesthesia.^{1,2} Anesthetic mortality in the past two decades is estimated to range from 0.05 to 10 per 10,000 administered anesthetics.³⁻⁹ The available knowledge on safety and quality of anesthetic care encompasses insight into the effects of anesthetic drugs and techniques and the anesthesia practice. However, quantitative estimates of how the characteristics of the anesthesia practice (hereafter referred to as *anesthesia management*) impact perioperative morbidity and mortality are limited. Anesthesia management entails a broad range of factors related to characteristics of the hospital and anesthetic department (operating room, preoperative and postoperative care unit, medical ward, intensive care unit), training and education, quality and quantity of physician and nonphysician staffing, availability and use of medical protocols, and standards for monitoring in the intraoperative and postoperative period. A few investigators have quantitatively studied the effect of the anesthesia management on adverse perioperative events.¹⁰⁻¹⁸ The safety and quality of perioperative care may be further improved by quantifying the risk of more factors related to anesthesia management. We performed a case-control study to assess 24-h postoperative severe morbidity and mortality after all types of surgery in relation to anesthesia management factors. The aim was to assess which anesthesia management factors are independent risk factors for perioperative severe morbidity and mortality and are amenable for preventive measures.

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Materials and Methods

A description of study methods has been reported previously.¹⁹ In brief, after obtaining institutional and ethical approval (Medical Ethical Committee, Leiden University Medical Center, Leiden, Zuid-Holland, The Netherlands), a case-control study within a prospectively defined cohort was performed. In all participating institutes, written information, oral information, or both were given to patients, informing them that for all patients undergoing anesthesia, a study was taking place in the hospital with the goal of increasing quality of care. Thus, patients were informed about the research and approved of the study.

Study Design

Given the objective to conduct a quantitative, etiologic study and in view of the rare occurrence of anesthesia-related deaths and unintentional comas, a case-control design was chosen. By identifying all cases with the outcome of interest and selecting controls for comparison, this technique is more efficient than a full-cohort study. Furthermore, it allows the identification of an etiologic relation between the outcome and multiple risk factors. Absolute event rates can also be obtained because information on the full cohort is available.²⁰⁻²⁵ In this study, the outcomes of interest were perioperative severe morbidity and mortality. Severe morbidity was defined as unintentional coma, persisting 24 h after anesthesia. Mortality was defined as death, during or within 24 h after undergoing anesthesia.

Therefore, cases were patients who remained comatose or died according to the aforementioned criteria irrespective of the presumed cause. Controls were patients who had not died and not remained comatose after having undergone anesthesia, randomly drawn from the cohort, matched for sex, and within the same 5-yr age group.

Study Cohort

The cohort comprised all patients undergoing anesthesia (general, regional, or a combined technique) from January 1, 1995, to December 31, 1996, in 3 of the 12 provinces in The Netherlands. Assuming that the prevalence of anesthesia management risk factors is 5% and that the incidence of perioperative death is 1:10,000, it was calculated that we would be able to show an increase in the risk of 5-15% with a power of 90% and a significance level of 5% with a study population of at least 500,000 patients. For practical and logistic reasons, it was decided that the study would be executed in a part of the hospitals in The Netherlands. It was also

evident that to be able to generalize the results to other clinical settings in The Netherlands and any developed country, the selected hospitals should be a valid reflection of a broad spectrum of anesthetic practices, e.g., the study area should include university, large peripheral (teaching and nonteaching), medium peripheral, and small peripheral (rural) hospitals. Therefore, after an inventory, three provinces in The Netherlands were selected: Zuid-Holland, Utrecht, and Gelderland. These provinces make up 35% of the total area of The Netherlands and include 55% of the Dutch population. The area comprises three of the largest Dutch cities, one out of five agricultural districts, and five out of eight teaching hospitals. Therefore, these are considered a valid reflection of Dutch anesthetic practice and perform approximately one third (400,000) of the total number of anesthetics performed yearly in The Netherlands (1.3 million \ddagger).

A group of anesthesiologists can form a structural (and financial) unit called an *anesthetic partnership* and can work at two hospitals. The total number of anesthetic partnerships in this area is 53, operating in 64 different hospitals. Sixty-one (95%) of the 64 eligible hospitals consented to participate at the start, and 58 (92%) actively participated for the entire study period. The total number of anesthetic procedures during the study period was 869,483. Information on 811 cases and 883 controls was collected during the study. Four cases were missing information on sex and age; these were excluded from further analysis.

Data Collection

Between July 1, 1994, and December 31, 1994, eligible hospitals were recruited and received a study protocol. Regional information meetings were set up. In each hospital, the approval of the anesthesiologists and the medical staff committee was required. The anesthesiologists were asked to approach a member of the medical staff, preferably not an anesthesiologist, to function as a "correspondent," i.e., as an intermediary between the anesthesiologists and the investigators. All cases, controls, and hospitals were known in the study center by a unique identification number to which only one of the investigators had access. All contact was made through the correspondent, thus preserving anonymity of the patient and anesthesiologist involved.

Data were collected by means of two structured questionnaires: the Hospital Characteristics Questionnaire (appendix 1) and the Procedure Questionnaire (appendix 2) and the anesthesia and recovery forms.

At the beginning and end of the study, the hospital characteristics questionnaire, with characteristics of the anesthetic practice and hospital, was submitted by each participating hospital. Thus, the incidence of 24-h severe morbidity and mortality could be calculated, and important changes in anesthetic practice could be accounted

\ddagger Dutch National Medical Registration and Information System on Hospital Care, 1997. From Prismant, Institute for Advice, Research and Information in Health Care, Utrecht, The Netherlands. Available at: <http://www.prismant.nl>. Accessed September 29, 2004.

for in the data analysis. During the 2 yr of the study, no major changes were established in the participating hospitals except for an increase in performed procedures. The reported numbers of anesthetics performed in a hospital at the start and at the end of the study were used in the incidence calculation. For some questions in the Procedure Questionnaire, it was checked whether they were in accord with the answers on comparable questions in the Hospital Characteristics Questionnaire (e.g., 24-h recovery room available, anesthetic nurse on duty).

For each case and control, a Procedure Questionnaire and anesthesia and recovery form were obtained.

The Procedure Questionnaire contained preoperative, intraoperative, and postoperative factors. Preoperative factors included patient-related factors (e.g., age, sex, American Society of Anesthesiologists physical status classification)²⁶ and anesthetic factors (e.g., preoperative assessment, type of premedication, equipment check). Preoperative and intraoperative surgical variables were patient admission status (clinically, or outpatient), time, duration, urgency (elective, nonelective, urgent), and type and complexity of the procedure (appendix 3). To determine the complexity of the procedure (minor, intermediate, or major) the classification proposed by Cohen *et al.*²⁷ was used.

Intraoperative and postoperative anesthesia management factors included presence of physician and non-physician staffing, type of anesthesia and anesthetics used, characteristics of induction, maintenance and emergence of anesthesia, and availability, checks and use of equipment, postoperative location, staffing, monitoring, and pain medication.

Selection of Cases and Controls

Immediately after a death or coma, the Procedure Questionnaire and an anonymous anesthesia and recovery form were submitted to the study center. As soon as a case was reported, a control was drawn from a randomly selected hospital using computer-generated tables of random numbers. The control was matched for sex and was aged within 5 yr of the case. The request for a control patient was made to the correspondent of the selected hospital by telephone and by letter. The correspondent ensured that the controls were randomly drawn from the operating schedule. Instructions were given on how to proceed in case no one, or more than one person, fulfilled the matching criteria. If at 1 week after the request no information on a control patient was received in the study center, the correspondent was reminded by phone and was prompted to supply the requested control. In selecting controls, the objective was to ensure that the dates of anesthesia for a case and matched control were as close as possible and that no preference for the time, type, or urgency of operation occurred. Therefore, controls represent a valid sample of the source population from which the cases emerged.

For data collection on cases and controls, identical Procedure Questionnaires were used, and anesthetic and recovery forms were obtained for both. By means of a unique identification number and the local correspondent, it was possible to ask for additional patient specific information (for cases and controls) if necessary.

Differences in risk factors for mortality and morbidity are to be expected between cases and controls. To allow valid assessment of anesthesia management-related determinants of mortality and coma, adjustment for remaining differences in risk factors between cases and controls that could act as confounders was achieved by multivariable modeling as outlined below. This is the method of choice and to be preferred above matching.²⁰⁻²⁵

Dutch Anesthesia Practice

Anesthesia practice in The Netherlands is based on a flexible one-on-one system in which one anesthesiologist, assisted by an anesthetic nurse or resident, is responsible for one anesthetized patient during induction and emergence of anesthesia. However, during maintenance, a two-on-one system is allowed, in which it is sufficient to have an anesthetic nurse or resident present in the operating room and an anesthesiologist at all times approachable in the vicinity. Therefore, one anesthesiologist is responsible for two anesthetized patients at the same time. The training of anesthetic nurses takes 3 yr. When qualified, they are allowed to manage anesthetic maintenance without an anesthesiologist, but not induction or emergence.

Statistical Analysis

Because comatose patients were too few to analyze separately and all initially comatose patients died in the hospital, the analysis was performed on controls ($n = 883$) and all cases ($n = 807$) jointly. Comparisons of patient, procedure, anesthesia, and hospital characteristics were tested with the Student *t* test, chi-square test, or Mann-Whitney U test as appropriate. Crude risks and 95% confidence intervals (CIs) of all preoperative, intraoperative, and postoperative factors for perioperative morbidity or mortality, estimated as the odds ratio, were calculated by univariate logistic regression. Because the main interest was in the causal relation between anesthesia management and perioperative coma and death, anesthesia management-related preoperative, intraoperative, and postoperative risk factors were considered potential determinants of the outcomes. Patient-, surgery-, and hospital-related factors were considered potential confounders of this relation.

Determinants were further tested if, in the univariate analysis, two-sided *P* values were less than 0.25 or if the variable seemed relevant (biologically or from an anesthesia management point of view). To adjust risk estimates of the determinants for confounders, multivariable logistic regression was used. Patient-, surgery-, and hospital-

related factors were considered possible confounders if they were significant in the univariate analysis or were judged to be biologically relevant. For each determinant significant in the univariate analysis, possible confounders were tested by multivariable logistic regression according to the method described by Hosmer *et al.*²⁸: The importance of each potential confounder included in the model was verified by the likelihood ratio test and a comparison of the estimated odds ratio of the determinant from models containing and not containing the potential confounder. A significant likelihood ratio test with a change of the estimated odds ratio was taken as evidence that a biologically plausible factor was a confounder. It was therefore included in the model. Subsequently, for each adjusted determinant, interaction of biologically plausible combinations of the determinant and one or more confounders was tested by the likelihood ratio test. A significant likelihood ratio test result for a model containing an interaction term compared to the model without resulted in inclusion of the interaction term in the model. For all models, goodness of fit was tested according to the Hosmer and Lemeshow test for goodness of fit. Thus, adjusted risks for anesthesia management factors were calculated, controlling for confounders. Patients with more than 10% missing values were excluded. The statistical analysis as described above was conducted using the Statistical Package for the Social Sciences, release 11.5.0 (SPSS Inc., Chicago, IL).

Results

The study population consisted of 807 cases and 883 controls, who all underwent anesthesia for a surgical procedure, except for one subject who underwent a radiodiagnostic procedure. Characteristics of the patients, surgical procedure, anesthetic technique, and hospital are presented in table 1. As expected, a higher proportion of the cases compared with the controls had a severe American Society of Anesthesiologists classification. Similarly expectedly, although the study was designed to ensure that controls were drawn without preference for the time, type, complexity, or urgency of operation, controls more often underwent minor, elective procedures during working hours. The mean duration of the procedure was significantly longer in the cases (mean difference, 1.18 h; SE, 0.10; $P < 0.01$). This was related to the surgical interventions performed. Cases more frequently underwent cardiac and major vascular procedures; controls more often underwent orthopedic, urologic, and ophthalmologic procedures.

Incidence of 24-h Postoperative Morbidity and Mortality

The total number of reported cases was 811. Of these, 769 (95%) died within 24 h, and 42 (5%) remained

comatose, all of whom eventually died in the hospital. The number of anesthetics in the study area and study period was 869,483. The estimated incidence of 24-h postoperative mortality was 8.8 (95% CI, 8.2–9.5) per 10,000 anesthetics, and the estimated incidence of 24-h postoperative coma was 0.5 (95% CI, 0.3–0.6).

Anesthesia Management-related Preoperative, Intraoperative, and Postoperative Risk Factors

Patient-, procedure-, and hospital-related factors in the univariate analysis significantly related to 24-h postoperative severe morbidity and mortality are presented in table 2.

Preoperative, intraoperative, and postoperative anesthesia management-related factors independently associated with 24-h postoperative severe morbidity and mortality were identified. Results of the univariate and multivariate analyses are presented in tables 3 and 4, respectively.

Factors that were determined to confound the association with anesthesia management factors and perioperative morbidity and mortality expectedly comprised the physical condition of the patient (age, sex, American Society of Anesthesiologists physical status classification), the surgical procedure (time, duration, urgency, type, and complexity), the anesthetic technique (general, regional, or a combined technique), and the hospital (number of beds, university or peripheral, referral, or teaching function).

Preoperative Anesthesia Management Risk Factors. Equipment check, performed with a checklist and protocol, was associated with a decreased risk of perioperative morbidity and mortality as opposed to other methods of equipment check, *e.g.*, no check, solely with checklist, solely with protocol (odds ratio, 0.64; 95% CI, 0.43–0.95). In accordance with the way equipment is checked, documentation of the check was similarly associated with a decreased risk (odds ratio, 0.61; 95% CI, 0.40–0.92) (table 4).

Intraoperative Anesthesia Management Risk Factors. Direct (intercom) availability of the anesthesiologist during maintenance compared with indirect (by means of telephone, beeper, or walkie-talkie) availability was associated with a significantly lower risk (odds ratio, 0.46; 95% CI, 0.31–0.66).

No intraoperative change of anesthesiologist by another was associated with a decreased risk (odds ratio, 0.44; 95% CI, 0.20–0.99). We checked whether this was influenced by the way information was exchanged between relieving anesthesiologists (not at all, by telephone, or in the operating room). However, this did not influence the association of intraoperative change of anesthesiologist on outcome.

The presence of an anesthetic nurse working full-time compared with part-time during maintenance was associated with a decreased risk (odds ratio, 0.41; 95% CI,

Table 1. Baseline Characteristics of the Study Population, the Surgical and Anesthetic Procedure, and the Hospital

Characteristic	Cases (n = 807)	Controls (n = 883)	Two-sided P Value
Mean age, yr	64.4 (62.8–65.0)*	63.6 (62.1–65.2)*	0.53
Sex, % women	38.5	42.9	0.06
ASA physical status, %			<0.01
I	2.2	30.6	
II	6.2	47.8	
III	21.8	19.9	
IV	30.3	1.5	
V	39.5	0.2	
Urgency of procedure, %			<0.01
Elective	21.5	87.4	
Nonelective	15.1	10.5	
Urgent	63.4	2.0	
Time of procedure, %			<0.01
During working hours (08:00–16:00 h)	50.7	96	
Outside working hours (<23:00 h)	32.3	3.4	
Outside working hours (>23:00 h)	17.1	0.6	
Duration of procedure, h	2.7 (2.5–2.9)*	1.5 (1.4–1.6)*	<0.01
Type of surgery, %			
General	42.6	28.5	
Vascular	19.9	7.5	
Orthopedic	9.0	19.8	
Urologic	2.2	12.8	
Gynecologic	0.2	4.6	
Obstetric	0.7	0.1	
Ophthalmologic	0.6	12	
Ear, nose, throat	0.6	2.2	
Cardiac	12.1	1.9	
Other thoracic	4.0	1.8	
Neurosurgical	6.5	4.0	
Trauma	0.7	0	
Plastic and corrective	0.4	2.6	
Mouth and jaw	0.2	1	
Radiodiagnostic procedures	0.1	0	
Complexity of the procedure, %			<0.01
Minor	3.7	26.3	
Intermediate	57	67.2	
Major	39.3	6.5	
Anesthetic techniques, %			
Regional	4.7	21.1	
Regional with sedation	5.1	13.8	
Inhalational	8.7	10.9	
Inhalational with sedation	0	0.2	
Total intravenous	29.2	9.3	
Combined intravenous and inhalational	46.5	33.4	
Regional with inhalational	1.4	2.8	
Regional with total intravenous	3.5	6.6	
Regional with combined technique	0.9	1.7	
Sedation	0.1	0.2	
Regional technique, %			
Epidural lumbar	3.2	6	
Epidural thoracic	2.0	2.7	
Epidural cervical	0.2	0	
Epidural caudal	0.1	1.4	
Spinal	8.4	25.3	
Plexus block	0	0.7	
Peripheral	0.9	9.4	
Spinal and epidural (lumbar)	0	0.6	
Type and size of hospital, %			<0.01
0–150 beds, nonteaching/nonuniversity	2.7	8.6	
151–300 beds, nonteaching/nonuniversity	4.2	14.7	
301–500 beds, nonteaching/nonuniversity	18.9	32	
>500 beds, nonteaching/nonuniversity	35.3	23.9	
<500 beds, teaching/university	3	4	
>500 beds, teaching/university	36	16.8	

* 95% confidence interval.

ASA = American Society of Anesthesiologists.

Table 2. Unadjusted Odds Ratios for Risk Factors for 24-h Postoperative Mortality and Coma

Risk Factor	Category	No. Missing	% Missing	Odds Ratio (Univariate)	95% CI	Two-sided P Value
Patient related						
Sex	Female	7	0.4	0.832	0.684–1.011	0.06
	Male (reference)			Reference		
Age, yr	1	9	0.5	1.001	0.997–1.006	0.53
	2			0.000	0.000–0.002	<0.01
	3			0.001	0.000–0.003	<0.01
ASA classification	3	7	0.4	0.006	0.002–0.026	<0.01
	4			0.118	0.026–0.528	<0.01
	5 (reference)			Reference		
Procedure related						
Time of procedure	Day	2	0.1	0.042	0.029–0.062	<0.01
	Evening–night (reference)			Reference		
Nature of procedure	Elective			0.008	0.005–0.013	<0.01
	Nonelective	2	0.1	0.046	0.027–0.079	<0.01
	Urgent (reference)			Reference		
Duration of procedure, h		20	1.2	1.465	1.364–1.573	<0.01
	Minor			0.023	0.014–0.037	<0.01
	Intermediate	2	0.1	0.139	0.102–0.189	<0.01
Complexity of procedure	Major (reference)			Reference		
Hospital related						
Type of hospital, no. of beds	0–150 nonteaching	0	0	0.147	0.088–0.245	<0.01
	151–300 nonteaching			0.133	0.087–0.203	<0.01
	301–500 nonteaching			0.274	0.207–0.362	<0.01
	>500 nonteaching			0.687	0.527–0.896	0.01
	<500 teaching/university			0.348	0.199–0.606	<0.01
	>500 teaching/university (reference)			Reference		

ASA = American Society of Anesthesiologists; CI = confidence interval.

0.24–0.70). In Dutch anesthetic practice, an anesthetic nurse is nearly always present. In very few instances was it noted that no anesthetic nurse was present during anesthesia. Therefore, a comparison without anesthetic nurse was not possible.

The presence of two persons compared to one person during emergence of anesthesia was associated with a decreased risk (odds ratio, 0.69; 95% CI, 0.47–0.99). We checked whether the risk was influenced by particular combinations of two persons at emergence, assuming that certain combinations would be stronger than others (e.g., a fully trained anesthesiologist and an experienced resident or anesthetic nurse). However, we were not able to show this beyond the fact that two persons being present decreased the risk. Furthermore, we checked whether this risk factor was influenced by the type of anesthetic technique performed, because many anesthesiologists consider regional anesthesia “not to be terminated” and are not present at emergence. However, anesthetic technique did not influence the risk.

At the end of anesthesia, reversal of the effect of muscle relaxants (odds ratio, 0.10; 95% CI, 0.03–0.31) and of the combination of opiates and muscle relaxants (odds ratio, 0.29; 95% CI, 0.18–0.48) were associated with a decreased risk. We checked whether this was influenced by the type of postoperative location (recovery room followed by ward, postanesthesia care

unit, or intensive care unit). However, no significant interaction with the postoperative location existed (table 4).

Postoperative Anesthesia Management Risk Factors. Postoperative administration of opiates (odds ratio, 0.165; 95% CI, 0.11–0.25), local anesthetics (odds ratio, 0.06; 95% CI, 0.01–0.40), and the combination of opiates and local anesthetics (odds ratio, 0.324; 95% CI, 0.14–0.75) as opposed to no pain medication was associated with a decreased risk of coma or death, adjusted for the confounders, mentioned above. This was most pronounced when they were administered intramuscularly (odds ratio, 0.13; 95% CI, 0.07–0.34) or epidurally (odds ratio, 0.23; 95% CI, 0.06–0.89) as opposed to intravenously. Neither risk factor was influenced by the type of postoperative location (recovery room followed by ward, postanesthesia care unit, or intensive care unit) as shown by lack of significant interaction (table 4).

Discussion

In this study, an association was established between perioperative coma and death and intraoperative presence of anesthetic personnel, administration of drugs intraoperatively and postoperatively, and characteristics of delivered intraoperative and postoperative anesthetic care.

Table 3. Unadjusted Odds Ratios for Anesthesia Management Risk Factors for 24-h Postoperative Mortality and Coma

Risk Factor	Category	No. Missing	% Missing	Odds Ratio (Univariate)	95% CI	Two-sided P Value	
Preoperative							
Equipment check	With protocol and checklist	3	0.2	0.594	0.489–0.722	<0.01	
	No check/check without protocol/with protocol (reference)			Reference			
Documentation of equipment check	Yes	106	6.3	0.591	0.484–0.721	<0.01	
	No (reference)			Reference			
Intraoperative							
Availability and reachability of anesthesiologist	Direct	18	1.1	0.604	0.484–0.755	<0.01	
	Indirect (reference)			Reference			
Intraoperative change of anesthesiologist by another	No	16	0.9	0.198		<0.01	
	Yes (reference)			Reference			
Presence of anesthetic nurse	Full-time working	6	0.4	0.876	0.659–1.166	0.37	
	Part-time working (reference)			Reference			
Presence at emergence and termination of anesthesia	Two persons	68	4	0.870	0.673–1.125	0.29	
	One person (reference)			Reference			
Reversal of anesthesia	Opiates	115	6.8	0.270	0.056–1.308	0.10	
	Muscle relaxants			0.236			0.102–0.547
	Opiates and muscle relaxants			0.220			
	No (reference)			Reference			
Postoperative							
Type of postoperative pain medication administered	Opiates	127	7.5	0.384	0.311–0.474	<0.01	
	Local anesthetics			0.108			0.024–0.488
	Combination			0.453			
	No (reference)			Reference			—
Route of administration of postoperative opiates	Epidural	40	2.4	0.131	0.076–0.226	<0.01	
	Intramuscular			0.077			0.054–0.111
	Intravenous (reference)			Reference			

CI = confidence interval.

To our knowledge, this is the first case-control study aimed at quantitative assessment of multiple risk factors related to anesthesia management for perioperative death. The advantages of the case-control design have been mentioned. However, this design has certain inherent difficulties relating to its validity, *e.g.*, sampling of cases and controls and definition of the source population. It is of major importance that cases should be ascertained independently of the determinants under study—in this case, the anesthesia management risk factors. To this aim, we decided to include every perioperative death and coma in the study area to ensure that no selection bias was introduced at the level of the individual hospital. This way, we could be certain that controls originated from the same study population as the cases and could therefore be used for a valid estimate of risk exposure in the population. The study population was defined by geographic region and circumscribed time frame, and we confined the study to severe outcomes only. Using severe outcomes improves the chances of complete data acquisition and minimizes the chance of a confounded relation between risk factors and the outcomes.

Controls were matched to cases to ensure on average similarity of distributions of age and sex. It is important to note that the motive for the procedure was not control of confounding (for which we used multivariable

regression analysis) but to improve statistical efficiency. Except for age and sex, no matching on other patient factors, type of surgery, etc. was done because this might introduce rather than reduce bias. Furthermore, matching (*e.g.*, on American Society of Anesthesiologists physical status classification) would preclude analysis of the matching factor as a risk factor.^{20–25}

In this study, a voluntary reporting system was used. The main drawbacks are selection bias and underreporting. In the introductory phase and throughout the study, the importance of submission of every perioperative coma and death was emphasized to prevent selection of presumed “anesthetic” cases. Furthermore, much attention was given to maintaining anonymity, confidentiality, and privacy of the participating anesthesiologists. Written assurance was provided by the Dutch Health Care Inspectorate to indemnify the investigators against revealing knowledge about events to the authorities and to legally secure confidentiality and privacy of the participating anesthesiologists. Thus, we expected to prevent a preferential submission of nonanesthetic cases. With respect to underreporting, no compulsory register of postoperative coma or deaths exists in The Netherlands. However, since the start of the study, one quarter of the participating hospitals used a check system to ensure that no patient fulfilling the study criteria was missed,

Table 4. Adjusted Odds Ratios for Anesthesia Management Risk Factors for 24-h Postoperative Mortality and Coma

Risk Factor	Category	Odds Ratio (Multivariate)	95% CI	Two-sided P Value
Preoperative				
Equipment check*	With protocol and checklist	0.640	0.432–0.948	0.03
	No check/check without protocol/with protocol	Reference		
Documentation of equipment check	Yes	0.607	0.399–0.923	0.02
	No	Reference		
Intraoperative				
Availability and reachability of anesthesiologist	Direct	0.455	0.313–0.662	<0.01
	Indirect (reference)	Reference		
Intraoperative change of an anesthesiologist by another†	No	0.444	0.199–0.990	0.05
	Yes (reference)	Reference		
Presence anesthetic nurse	Full-time working	0.408	0.236–0.704	<0.01
	Part-time working (reference)	Reference		
Presence at emergence and termination of anesthesia	Two persons	0.687	0.474–0.996	0.05
	One person (reference)	Reference		
Reversal of anesthesia	Opiates	0.636	0.100–4.027	0.63
	Muscle relaxants	0.101		
	Opiates and muscle relaxants	0.290		
	No (reference)	Reference		
Postoperative				
Type of postoperative pain medication administered	Opiates	0.165	0.108–0.254	<0.01
	Local anesthetics	0.061		
	Combination	0.324		
	No (reference)	Reference		
Route of administration of postoperative opiates‡	Epidural	0.226	0.057–0.887	0.03
	Intramuscular	0.130		
	Intravenous (reference)	Reference		

* All risk factors are adjusted for characteristics of the patient (age, sex, American Society of Anesthesiologists classification), the surgical procedure (time, duration, urgency, type, and complexity), the anesthetic procedure (general [inhalational, total intravenous, combined technique], regional, or a combination; type of regional anesthesia), and the hospital (type and size). † Also corrected for transfer (not done, by telephone, in the operating room) of patient information between exchanging anesthesiologists. ‡ Also adjusted for the type of pain medication administered and postoperative location.

CI = confidence interval.

using local existing registries. The hospitals with a check system varied from small to major teaching hospitals. This allowed an estimate of underreported cases. Estimated underreporting ranged from 13 to 47%, taking into account type and size of the hospital. However, the question is whether underreporting could have led to spurious associations between anesthesia management factors and outcome. This is only the case if there is evidence that underreporting was selective, *e.g.*, that specific cases would have been reported (*e.g.*, the ones specifically related or unrelated to anesthesia management) and others not. It is difficult to estimate the selectivity in the underreporting. Some members of the steering committee checked during the study in their own hospital whether questionnaires were filled in correctly. No major faults potentially resulting in bias were encountered.

Another concern is bias in obtaining the needed information: information bias. Information on cases and controls is obtained after the status of a patient is established (*e.g.*, the case has died and the control was asked after the anesthetic procedure). It is conceivable that the recall of the anesthesiologist is different for cases and controls. We made the postoperative time span relatively short (only 24 h) and comparable for cases and controls. Moreover, at admission at the study center, we compared the questionnaire with the anesthetic and recovery

form. By means of a unique identification number of the hospital and case or control, it was always possible to obtain additional information. Furthermore, it is also conceivable that the recall was adequate but the documentation on the form was not correct. With an intensive introductory phase, regular informative meetings, and a regular informative newsletter, we hope to have increased compliance and enthusiasm and reduced fear of legal consequences and thus selectivity in the documentation of the actual perioperative period. However, if selectivity existed, this type of bias would probably serve to underestimate an effect.

Our main interest was in the relation of anesthesia management-related risk factors and perioperative coma or death. Therefore, our questionnaire contained 200 questions on anesthetic management. For approximately 10% of the risk factors, multiple questions at different sites were included, thus serving as a check. Furthermore, we were able to check a substantial proportion of the factors from the questionnaire by means of the anesthetic and recovery form. In our etiologic analysis, an anesthetic risk factor and the combination of the anesthetic risk factor and its confounders had to be plausible, both biologically and in daily anesthetic practice.

In our study, it was found that equipment checks performed with protocol and a checklist decreased the

risk. Since the publication of a checklist for the preoperative check of anesthetic machines in 1990,^{29,30} there has been concern about widespread failure to perform adequate preoperative checks of anesthetic machines. This is despite most anesthesiologists' being aware of the guidelines and of the importance of checking anesthetic equipment before use. Kendall *et al.* showed that in 60–82.5% of machines checked, at least one fault was present, of which 11–18% were deemed serious.^{29,30} Several authors have suggested that the most important reason for failure to follow the guidelines is that they are perceived as too time consuming.^{31–33} Therefore, the equipment checks and their guidelines must be a compromise between safety and practicability. Surprisingly, in our study, it was not found that reported actual equipment failure contributed to perioperative deaths. We can only speculate on the significance of the two risk factors (equipment check and its documentation) that are in accord with each other. The possibility to perform such a preoperative equipment check may reflect the acuteness of the procedure. However, the difference remained after adjustment for all indicators of the acuteness of the procedure and severity of the preoperative condition of the patient. Therefore, this risk factor could be a measure of experience, level of education, and composition of the anesthetic care team. We depended on a voluntary reporting system, so it is conceivable that bias could have been introduced. First, in accord with the literature,³⁴ one would expect that in the nonelective and urgent procedures, time would have been limited to adequately perform and document an equipment check. Second, a tendency could have existed to fill in "correct" answers, especially for the patients who died after anesthesia. However, in that case, a risk difference between cases and controls would have disappeared.

Failure to perform an equipment check was also frequently cited as a risk factor by investigators of critical incidents.^{35–42} This partly reflects the role of actual equipment failure, reported to occur in 15–20% of the procedures, but probably also refers to overall quality of care.

As hospitals and physicians adapt to new financial challenges, the mix of healthcare providers has been changing. It is suggested that the best outcomes may occur when anesthesia is provided by an anesthesia care team.⁴³ However, there are limited outcome data regarding provider models in specific areas, such as perioperative care. Silber *et al.*^{14,15} reported that the mortality rate and failure to rescue were lower when anesthesiologists directed anesthesia care and the anesthesiologist was board certified. Aiken *et al.*^{16,17} found that a lower nurse-to-patient ratio and higher level of education of the nurses decreased postoperative mortality and failure to rescue. These studies, among others,^{43,44} confirm that the presence of anesthetic personnel plays an important role in the occurrence of adverse events and failure to rescue after surgical interventions. Our results on intra-

operative presence of anesthetic personnel (sc. direct availability and intraoperative change of anesthesiologist, presence at emergence, presence of a full-time working anesthetic nurse) are consistent with the results of these studies: Direct availability of the anesthesiologist decreases the risk of postoperative mortality and coma. Also, intraoperative changing of anesthesiologists seems unfavorable for the patient. This seems to be in contradiction with the findings from an analysis of relief-associated incidents by Cooper *et al.*⁴⁵ They concluded that none of the incidents with negative outcome were caused by a relieving anesthesiologist and that change may be beneficial by discovery of incidents. For minor incidents, relief of the anesthesiologist may result in early discovery of incidents that do not directly lead to serious adverse outcomes and would have been discovered and solved anyway. For serious adverse outcomes, our finding probably exposes another aspect, *e.g.*, the importance of the level of education and clinical experience as an influence on overall patient care. The importance of education and experience, as well as an adequate personnel-to-patient ratio, is supported by our finding that the presence of two persons at emergence compared with one decreases the risk. At emergence from anesthesia, it is important to have enough personnel available to facilitate patient care. We checked whether this risk was influenced by particular combinations of the anesthesia care team at emergence. However, we were not able to show this, although the two persons were nearly always a combination of a medical and a nonmedical anesthetic team member. The observation that the presence of a full-time working anesthetic nurse is preferable may lead to future research into the question of whether there is enough effort to keep part-time personnel motivated and updated.

The reversal of the effect of opiates and muscle relaxants seems to decrease the risk. The effect of muscle relaxants, especially the postoperative effect on respiration, has been studied since their first introduction. We were not able to determine that unsuspected respiratory failure was the cause of death of our case patients, although five were found unexpectedly dead in bed on the ward. Unfortunately, no autopsy was performed in these cases, so we can only speculate on the cause of death. Although we adjusted in the analyses for postoperative location, it remains possible that inadequate postoperative care contributed to the adverse effect of lack of reversal.

The reduction of risk by postoperative administration of opiates, local anesthetics, or a combination may be explained by the reduction of postoperative pain and stress. The concomitant finding that intramuscular administration of opiates, compared with intravenous administration, is more beneficial for the patient may be explained by the increased risk of respiratory problems during intravenous administration in conjunction with inadequate postoperative care facilities.

Knowledge of postoperative neurologic morbidity is limited. Postoperative comatose patients were few, prompting us for the purpose of the statistical analysis to include them among those who died. The estimated incidence of 24-h postoperative coma was 0.5 (95% CI, 0.3–0.6). This is comparable with the incidence reported in the literature. In 1993, Moller *et al.*^{10,11} (in the Danish pulse oximetry studies) showed that anesthesia was a contributory factor to 7-day postoperative mortality in 1 in 3,365 patients. Furthermore, they reported an incidence of postoperative coma in the pulse oximetry group of 0.01% and in the control group of 0.06%, and the overall postoperative incidence in both groups was 0.08%. Additional reports of postoperative neurologic complications by the International Study of Post-Operative Cognitive Dysfunction investigators pertain to postoperative cognitive dysfunction and not coma.⁴⁶

Although anesthetic practice in The Netherlands may differ in some aspects from practice in other countries, we believe that the factors we found to be associated with an increased risk of coma and death, notably general presence during anesthesia of anesthetic personnel and quality of delivered care, are applicable to other countries because they are independent of a specific anesthetic practice. Furthermore, so far, quantitative methods have been limited as applied to study the relation between factors related to anesthetic management and perioperative adverse events, but our study showed that they can be applied to increase insight into anesthetic risk factors.

In conclusion, perioperative mortality and morbidity are still substantial. Etiologic insight into the role of anesthetic management is limited and must be increased because certain aspects of anesthetic management, which are potentially eligible for preventive measures, continue to play a major role in adverse events.

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Appendix 1: Hospital Characteristics Questionnaire§§

- I. General Information on Hospital
 1. Number of beds
 2. Specialties
 - Surgical
 - Nonsurgical
 3. Number of operating rooms
 - Clinical
 - Day-care
 - Outpatient
 - Other areas in which anesthesia is administered
- II. Anesthetic Practice
 1. Staffing
 - Physician
 - Board certified anesthesiologists
 - Residents
 - Nonphysician
 - Board certified anesthetic nurses
 - Anesthetic nurses in training
 2. Daily practice
 - Presence of anesthetic nurses during maintenance
 - Presence of anesthetic nurse during duty
- III. Equipment
 1. Availability
 2. Maintenance
 - According to schedule
 - Responsibility
 3. Check of new equipment
- IV. Organization of Pre- and Postoperative Care
 1. Logistics of urgent or emergency procedures
 2. Recovery room
 - Availability of 24-h recovery room
 - Monitoring: which available
 3. Intensive care
 - Availability
 - Involvement anesthesiologist
 4. Trauma protocol
 - Involvement anesthesiologist
 5. Resuscitation protocol
 - Involvement anesthesiologist

§§ This information was collected for each participating hospital at the beginning and the end of the study.

||| This information was collected for all cases and controls.

Appendix 2: Procedure Questionnaire|||

- I. Patient- and Surgery-related Information
 1. Patient characteristics
 2. Date, time, and duration of surgical intervention
 3. Type and site of surgical intervention
- II. Staffing
 1. Presence of board-certified anesthesiologist
 - Details on board certification
 - During which phase of anesthesia
 2. Presence of non-board-certified anesthesiologist
 - Details
 - During which phase of anesthesia
 3. Presence of residents
 - Details on training program
 - During which phase of anesthesia
 4. Presence of board-certified nonphysicians
 - Details on board certification
 - During which phase of anesthesia
 5. Presence of non-board-certified nonphysicians
 - Details
 6. Intraoperative relief of physician staffing
 - Details
- III. Preoperative Care
 1. By whom
 2. Documentation
 3. Fasting protocol
 4. Preoperative pharmacological agents
- IV. Additional Information on the Surgical Procedure
 1. Patient admission status (clinical, daycare, outpatient)
 2. Type of surgical intervention (elective, nonelective, urgent)
- V. Equipment
 1. Checks
 - Executor
 - Realization
 2. Availability
 - Which monitoring devices
 3. Use intraoperatively
 - Which monitoring devices
- VI. Intraoperative Care
 1. Induction
 - Location
 - Physician staffing
 - Presence
 - Nonphysician staffing
 - Presence
 - Anesthetic technique
 - Anesthetics
 - Airway management
 2. Maintenance
 - Physician staffing
 - Presence
 - Nonphysician staffing
 - Presence
 - Anesthetic technique
 - Anesthetics
 - Respiration and ventilation
 3. Emergence
 - Location
 - Physician staffing
 - Presence
 - Nonphysician staffing
 - Presence
 - Pharmacological agents used

- VII. Documentation of Anesthesia
 - 1. Executor
 - 2. How executed
- VIII. Recovery Period
 - 1. Location
 - 2. Physician staffing
 - Presence
 - 3. Nonphysician staffing
 - Presence
 - 4. Monitoring
 - Availability
 - Use
 - 5. Pharmacological agents used
 - 6. Medical transfer of relevant information
 - 7. Documentation of recovery period
- IX. Problems and Adverse Events within 24 h
 - 1. Did any problems occur during or within 24 h after undergoing anesthesia?
 - Yes: fill in an additional questionnaire
 - No: end

Appendix 3: Definitions of the Urgency of the Procedure, Patient Admission Status, and Complexity of the Surgical Procedure

- I. Urgency of the procedure
 - Elective: A procedure that is planned in advance
 - Nonelective: A procedure in which the patient's condition suggests that the procedure has to be performed within 24 h
 - Urgent: A procedure in which the patient's condition suggests that the procedure has to be performed as soon as possible
- II. Patient Admission Status
 - Clinical: An intervention that is planned to be executed in a clinical setting in which a patient is admitted to hospital
 - Outpatient: An intervention that is performed without planned admission to hospital
- III. Complexity of the procedure
 - Major: Intracranial, major vascular, or intrathoracic
 - Intermediate: Intraabdominal, extremities, trunk, spine, or other head and neck
 - Minor: Eye, ear, nose and throat, perineal, endoscopy, and other sites