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SPECIAL ARTICLE

Risk factors for anaesthetic-related death in cats: results from the confidential enquiry into perioperative small animal fatalities (CEPSAF)†

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Background. Cats are commonly anaesthetized in veterinary practice, but recent figures describing the frequency of or risk factors for anaesthetic-related death are not available. The aims of this study were to address these deficiencies.

Methods. A nested case–control study was undertaken in 117 UK veterinary centres. All anaesthetic and sedation procedures and anaesthetic and sedation-related deaths (i.e. 'cases') occurring within 48 h were recorded. Details of patient, procedure, and perioperative management were recorded for all cases and randomly selected non-deaths (controls). A detailed statistical model of factors associated with anaesthetic and sedation-related death was constructed.

Results. Between June 2002 and June 2004, 175 deaths were classified as anaesthetic and sedation-related and 14 additional deaths (with insufficient information to be excluded) were included for the estimation of risk. During the study, 79 178 anaesthetic and sedation procedures were recorded and the overall risk of anaesthetic and sedation-related death was 0.24% (95% CI 0.20–0.27). Factors associated with increased odds of anaesthetic-related death were poor health status (ASA physical status classification), increasing age, extremes of weight, increasing procedural urgency and complexity, endotracheal intubation, and fluid therapy. Pulse monitoring and pulse oximetry were associated with reduced odds.

Conclusions. The risk of anaesthetic-related death in cats appears to have decreased since the last published study in the UK. The results should aid the preoperative identification of cats at greatest risk. Greater care with endotracheal intubation and fluid administration are recommended, and pulse and pulse oximetry monitoring should be routinely implemented in cats.

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Anaesthetic complications have been evaluated infrequently in veterinary practice.[1] The last UK study of veterinary anaesthetic small animal complications was undertaken in the 1980s and documented the risk of anaesthetic-related death in cats to be approximately 0.29%. Subsequent international work has reported the risk of anaesthetic-related death in cats to be approximately 0.1–0.2%.[2–4] This is substantially higher than that reported in human anaesthesia, where the risk of anaesthetic-related death (death where anaesthesia could not be reasonably excluded as a contributory factor) is approximately 0.02–0.05%.[5–7]

Identification of major risk factors for anaesthetic-related death could aid the reduction of complications. Previous studies identified poor health status, administration of the alpha$_2$ agonist xylazine, endotracheal

†This article is accompanied by Editorial II.

intubation, and lack of a technician monitoring the anaesthetic as factors associated with perioperative mortality in cats.[3 8 9] Since these studies, new drugs, monitoring, and anaesthetic techniques have been introduced into veterinary practice. On the basis of clinical experience and this previous work, we hypothesized that sick patients (ASA status III–V), the use of medetomidine and endotracheal intubation are associated with increased odds, whereas the use of acepromazine, propofol, isoflurane, intraoperative fluid therapy, and having a separate person monitor anaesthesia are associated with a reduction in the odds of anaesthetic-related death. Hence, the aims of this study were to estimate the current risk of death, to test the stated hypotheses, and to identify other current risk factors associated with anaesthetic-related death, in order to improve feline anaesthesia.

Methods

A pilot study was undertaken between June and October 2002 to refine *a priori* hypotheses, to test the methods and data collection tools, and to check the sample size calculations. Sample size calculations indicated that approximately 150–170 cases would be required to detect risk factors with a prevalence of 5% in the controls and an odds ratio of $\geq$2.5 or a prevalence of 10% in the controls and an odds ratio of $\geq$2.0 (80% power, 5% level of statistical significance, case:control ratio of 1:4). In the main study, a case–control study was undertaken nested in a cohort (i.e. a 'nested' case–control study) of all cats anaesthetized and sedated at participating veterinary practices and referral institutions in the UK (confidential enquiry into perioperative small animal fatalities, CEPSAF) (Appendix A).

In the cohort study, all general anaesthetics and sedations and outcomes at 48 h (alive, dead, or euthanased) were recorded prospectively by the centres on self-administered questionnaires. Anaesthesia was defined as chemical restraint, sufficient to allow endotracheal intubation. Sedation was defined as chemical restraint insufficient to allow endotracheal intubation had intubation been attempted, and represented mild tranquillization through to heavy sedation where the patient was unresponsive to minor to moderate stimuli, in sternal or lateral recumbency. Anaesthetic and sedation-related death ('cases' in the case–control study) was defined as perioperative death (including euthanasia) within 48 h of termination of the procedure, except where death was due solely to the surgical or pre-existing medical condition, such that anaesthesia or sedation could not be reasonably excluded as a contributory factor. An independent review panel, consisting of three specialist level veterinary anaesthetists and one specialist level veterinary surgeon, classified all potential deaths as anaesthetic and sedation-related or not. Deaths for which insufficient information was available for the independent review panel to allow classification were included as anaesthetic-related for the estimation of risk of death. The risk of anaesthetic and sedation-related death and 95% confidence intervals (95% CI) were calculated adjusting for clustering at the clinic level.[10 11] Further details relating to the cohort study are reported elsewhere.[12]

In the case–control study, cases were compared with anaesthetics or sedations recorded in the cohort that did not die within 48 h of the procedure (controls) (Appendix A). Details of the patient, procedure, anaesthetic and sedative management, and personnel involved were recorded for cases and controls on self-administered questionnaires (Table 1). Intended procedure type and duration were recorded, in addition to actual procedure and duration. In cases that died before the procedure was performed, intended duration was recorded as the mean duration for controls of the same procedure category. The unmatched controls were randomly and prospectively selected at a 1:4 case:control ratio from the cohort of cats anaesthetized and sedated during the study. The cohort study data were returned to the investigators on a monthly basis and were entered into a relational database (Access, Microsoft), exported to a spreadsheet (Excel, Microsoft) and cumulative frequencies of monthly anaesthetic and sedation events were calculated. This allowed the identification of individual cat anaesthetic and sedation events by veterinary centre and within that centre by animal number of the month (e.g. 53rd cat of 112 cat anaesthetics and sedations recorded that month at centre 1115). The controls were identified by centre, procedure number of the day, day of the week, and week of the month based on the previous month's distribution of procedures. Control questionnaires

Table 1 Risk factors evaluated in the case–control study

Patients details
Breed, sex, age, weight (including method of assessment)
Primary or referred patient
Previous anaesthetics and sedations in the last month
Preoperative evaluation and preparation
Patients' health status (ASA status) and pre-existing disease
Preoperative clinical examination, workup, and preparation
Procedure
Procedure urgency
Intended and actual procedure
Location of procedure and patient recumbency
Anaesthetic and sedative drugs administered
General anaesthesia or sedation
Premedication, induction, maintenance, and other drugs administered (including dose and route of administration)
Endotracheal intubation, anaesthetic breathing system used, and type of ventilation employed
I.V. catheter placed, perioperative fluid therapy given
Anaesthetic machine check performed
Monitoring
Person monitoring the patient and other duties of this person
Methods of monitoring and presence of a written record
Recovery
Duration of procedure, times to sternal recumbency and standing
Quality and location of recovery
Personnel involved and frequency of postoperative monitoring
Postoperative temperature taken
Personnel details
Person undertaking procedure, experience, and qualifications
Person monitoring the anaesthetic, experience, and qualifications

were requested shortly after the selected anaesthetic or sedation event had taken place.

Univariable screening of the association of the risk factors with anaesthetic and sedation-related death was undertaken by standard methods.[13 14] Biologically important factors and statistically significant variables ($P<0.2$) were evaluated in a multivariable mixed effects logistic regression model using a manual forward selection approach (Stata 7.0, Statacorp).[14] Continuous variables were evaluated for linearity, for higher order associations, and as fractional polynomials.[15] Clinic identity was treated as a random effect in the mixed model to account for clustering of outcome at this level. First-order interactions were assessed, and final model fit was checked using the Hosmer–Lemeshow test statistic, delta beta, and delta deviance influence diagnostic statistics.[14]A sample of 20% of the non-responding controls was compared with the controls for major risk factors to assess the likely representativeness of the controls. Statistical significance was set at the 5% level.

Results

Between June 2002 and June 2004, 175 anaesthetic and sedation-related deaths were recorded across 117 participating centres in the UK within 48 h of anaesthesia and sedation. An additional 14 deaths, for which insufficient information was available to classify them as anaesthetic-related, were included as anaesthetic and sedation-related deaths for the estimation of risk. Eighty-one deaths were ASA grade I–II (46%), 42 ASA grade III (24%), and 52 ASA grade III–V (30%) (Table 2). During the study, 79 178 cats were anaesthetized and sedated. The risk of anaesthetic and sedation-related death was 0.24% (95% CI 0.20–0.27). Further details relating to the cohort section of the study are reported in a companion paper.[12]

In the case–control study, 175 cases (14 indeterminate deaths were excluded here) were compared with 555 randomly selected controls. The mean weight (SD) of controls and cases were 3.8 (1.0) and 4.0 (1.4) kg, respectively.

Table 2 Mixed effects logistic regression model of the odds of anaesthetic and sedation-related death in cats. *Trend represents the OR for a one-category increase in the risk factor. Number of observations 723 out of 730

Risk factor	Categories	Cases (number of cats)	Controls (number of cats)	β	SE β	Odds ratio (OR)	95% Confidence interval	P-value
Health status (ASA grade)	ASA I–II	81	508					
	ASA II	42	39					
	ASA IV–V	52	8					
	Trend*			1.16	0.23	3.2	2.0–5.0	<0.001
Urgency of procedure	Scheduled	83	458					
	Urgent	67	89					
	Emergency	25	8					
	Trend*			0.46	0.23	1.6	1.0–2.5	0.050
Intended procedure	Minor procedure	115	520			1		
	Major procedure	60	35	1.00	0.35	2.7	1.4–5.4	0.005
Age	0–0.5 yr	6	24	−0.97	0.93	0.4	0.1–2.4	
	0.5–5 yr	54	287			1		
	5–12 yr	59	153	0.51	0.29	1.7	0.9–3.0	
	12 yr–max	56	84	0.73	0.32	2.1	1.1–3.9	0.058
	Unknown	0	7					
Weight	0–2 kg	9	5	2.75	0.85	15.7	2.9–83.6	
	2–6 kg	144	518			1		
	6 kg–max	19	17	1.03	0.50	2.8	1.1–7.4	
	Unknown	3	15	0.11	0.81	1.1	0.2–5.5	0.002
Endotracheal (ET) intubation	No ET tube	27	195			1		
	ET tube	148	360	0.66	0.33	1.9	1.0–3.7	0.042
Pulse and pulse oximeter used	None	49	100			1		
	Pulse assessed only	56	223	−1.10	0.34	0.3	0.2–0.6	
	Pulse oximeter used only	27	91	−1.62	0.43	0.2	0.1–0.5	
	Pulse and pulse oximeter	43	141	−1.81	0.40>	0.2	0.1–0.4	<0.001
Perioperative i.v. fluids	No fluids given	65	439			1		
	I.V. catheter used only	5	33	−0.34	0.65	0.7	0.2–2.5	
	I.V. fluids given	105	83	1.37	0.30	3.9	2.2–7.1	<0.001
Intercept				−5.03	0.58			
Random effect of clinical identity (ρ)				0.08 (ρ)	0.02 (SE)			0.054

Controls tended to be younger than cases: median age (inter-quartile range) 3.0 (0.7–9.3) and 7.9 (2.4–12.6) yr, respectively. Most cats were premedicated before the procedure (71% of controls, 69% of cases). The majority of patients' tracheas were intubated (65% of controls, 85% of cases, endotracheal tube size 3–5), and most of these had local anaesthetic spray (lidocaine/prilocaine mixture) used to desensitize the larynx. Muscle relaxants were rarely used in the cats either on induction or during maintenance of anaesthesia. Anaesthesia was primarily maintained with isoflurane (59% of controls, 75% of cases), though injectable methods of maintenance were also common (34% of controls, 21% cases). Cats generally breathed spontaneously during the procedure (98% of controls, 85% of cases) and oxygen supplementation was provided in 76% of controls and 90% of cases. Patient temperature was rarely measured (1–2% during the procedures, and after operation 11–15% of cats). I.V. fluid therapy was administered to 15% of controls and 60% of cases. Procedures were short [median (inter-quartile range)]: 25 (15–45) min in the controls, 30 (15–60) min in the cases, and included diagnostic procedures, routine neutering, dental surgery, fracture repair, and exploratory laparotomy.

In the multivariable model (Table 2), increasing ASA status, procedural urgency, major *vs* minor intended procedures, increasing age, extremes of weight, endotracheal intubation, and the use of fluid therapy were associated with increased odds of anaesthetic and sedation-related death. Pulse and pulse oximetry monitoring were associated with a reduction in odds. Increasing ASA physical status by one category (ASA I–II to ASA III and ASA III to ASA IV–V) was associated with a three-fold increase in odds of death. An increase of one increment in urgency (scheduled to urgent to emergency) was associated with a 1.6-fold increase in odds. Increasing age was associated with increasing odds, with cats 12 yr and older twice as likely to die as young adults (0.5–5 yr). Though the significance level of categorical age was just above the 5% level in the multivariable model (P=0.058), age was retained in the model on biological grounds and because it improved model fit. Cats weighing less than 2 kg were nearly 16 times as likely to die as those between 2 and 6 kg and cats 6 kg and above were nearly three times more likely to die. No breed associations were observed. Cats presenting for major procedures were nearly three times as likely to die as those presenting for minor procedures, and endotracheal intubation was associated with a two-fold increase in odds of death. Patients receiving fluid therapy were nearly four times as likely to die as those that did not, whereas cats that had pulse or pulse oximetry monitoring during the procedure were three to four times less likely to die than those that did not. After adjusting for other variables, particularly ASA physical status and intended procedure, the odds associated with sedation *vs* general anaesthesia were not significantly different and no drug associations were observed.

The response rate was good (94% of cases and 80% of controls). The non-responding controls were comparable with the responding controls for a number of major risk factors (Appendix B). Cases were clustered at the clinic level (P=0.05), and clinic was retained as a random effect. The fit of the logistic regression model was good as assessed by the Hosmer–Lemeshow goodness-of-fit statistic (P=0.90), the delta beta diagnostic statistic (all delta betas $<$1.0) and the delta deviance diagnostic statistic (all delta deviances $<$9.0, only seven covariate patterns $>$7.0).[14]

Discussion

This study represents the first large-scale multi-centre study of anaesthetic-related deaths in small animals in the UK, since the mid-1980s and documents a reduction in risk of death in cats compared with this previous work (0.24%, 95% CI 0.20–0.27, compared with 0.29%, 95% CI 0.22–0.37%).[8] Veterinary practices involved in the current study were anaesthetizing a sicker population of patients than in the previous study (8% compared with 4% ASA status III–V), suggesting that the improvements were greater than reflected in this overall risk of death. However, the risk of death was nearly 10 times greater than the risk of anaesthetic-related death reported in human anaesthesia (0.02–0.05%).[5 7 16] Cats are relatively small, with a large surface area to volume ratio, making them more prone to hypothermia and, potentially, to drug overdose than larger species. They have small airways and a sensitive larynx predisposing to upper airway complications.[17] Nonetheless, a major component of this greater risk in cats was likely to reflect different standards of anaesthesia. Fluid and ventilatory support were infrequent in the anaesthetized cats. Patient monitoring was often superficial with less than 10% of cats being monitored with capnography, electrocardiography, or arterial pressure measurement. Further, a specialized anaesthetist was generally not in charge of the anaesthetic, and dedicated postoperative and intensive care facilities were not available for the majority of patients.

A number of risk factors were identified that could aid preoperative patient assessment and identify those patients at greatest risk before anaesthesia. Patient health status, as described by ASA status, was particularly important. Though created for risk categorization in man, this study provides further support for the relevance of the ASA status to species other than man when assessing the risks of anaesthesia. The major association between health status and anaesthetic-related death has been previously documented in veterinary reports[3 8 18–20] and is consistent with that published in medical journals.[7 21–27] Pre-existing pathology may reduce the therapeutic index of administered anaesthetics, predispose to cardiopulmonary depression, and depress other physiological functions significantly. Additionally, procedural urgency could be a valuable factor to aid preoperative patient assessment. Increased risk has been associated with increasing urgency in human and equine anaesthesia,[7 22 24 27–30] and this was likely to reflect the ability to assess and stabilize patients before operation, and due to the tendency for urgent procedures to be presented outside of normal working hours, to reflect staffing levels and personnel fatigue. Greater attention to preoperative assessment of patient health status and procedural urgency and improved stabilization before the procedure could substantially reduce deaths.

Increased odds of anaesthetic-related death with increased patient age has not been reported before in cats, in contrast to work in canine,[20] equine,[18 30] and human anaesthesia.[7 22 23 25 26] The lack of an association with age in previous studies in cats was more likely to reflect limits of study power, than species-specific differences.[3 8 9] Old patients may be more susceptible to the depressant effects of anaesthetics, to hypothermia via impaired thermoregulatory mechanisms, and to prolonged recovery due to tendencies to reduced metabolic function and hypothermia,[31–33] and particular care should be taken when anaesthetizing these patients.

Increased odds of death seen with small patients were consistent with findings in dogs[34] and in paediatric anaesthesia.[35] Smaller patients could be more prone to drug overdose, to hypothermia, and to perioperative management difficulties (e.g. i.v. catheter placement, endotracheal intubation). Increased risk with increasing weight was likely to reflect, at least in part, risks associated with obesity. Obesity could contribute to perioperative complications via increased potential for respiratory compromise, reduced cardiovascular reserves, and slower recoveries after inhalation anaesthesia due to a greater sink for the inhalation agent.[36] These findings were not likely to reflect major confounding by age, as the association with weight was adjusted for age in the multivariable model. Interestingly, no breed association was observed. Increasing risk for patients presenting for major compared with minor procedures was also consistent with work in canine,[34] equine,[18 30] and human anaesthesia.[22 27 28] More complex and invasive procedures were likely to impose greater stress on patient physiology and when assessing patient risk before anaesthesia, assessment of the planned procedure's complexity should be considered.

Increased risk of major complication with tracheal intubation has been previously reported in cats,[3 8] and problems with airway management have also been a major cause of anaesthetic death in human anaesthesia.[7 16 37 38] In the current study, this association remained even after adjusting for major confounders, in particular ASA physical status and intended procedure, such that even in the healthier patients and the more minor procedures, increased odds ratios were observed when endotracheal intubation was undertaken. In the multivariable model, there was a non-significant tendency to an interaction between intended procedure and endotracheal intubation, with endotracheal intubation being particularly associated with increased odds of death in minor procedures and reduced odds in major procedures (endotracheal intubation OR=2.3 in minor procedures, OR=0.6 in major procedures, P=0.08).

The cause of death of cats that had had endotracheal intubation was most often categorized as of respiratory or cardiovascular origin,[12] and airway complications could have contributed in many of these cases. The feline airway is small and more sensitive to trauma, spasm, and oedema than that of the dog or horse[17 39] and as such the process of intubation, if not properly performed would be expected to increase complications. More cases that were intubated died after operation than those that were not (63% of cats that died after operation had endotracheal intubation compared with 48% of non-intubated cats), suggesting laryngeal trauma, spasm, or oedema may have been a more common contributory cause than endotracheal tube obstruction. Topical local anaesthesia was routinely used in the vast majority of cats in this study to desensitize the larynx before anaesthesia, whereas neuromuscular block to facilitate endotracheal intubation or maintenance of anaesthesia is not extensively practised in feline anaesthesia. Although more work is merited to evaluate this association further, the results suggest that endotracheal intubation should be used cautiously in cats undergoing minor procedures whereas for more complex procedures the provision of a patent airway remains more important.

The four-fold increase in odds associated with receiving fluid therapy was surprising. This has not been reported before in animals, was counter-intuitive, and may reflect residual confounding, particularly by health status, age, procedure type, and duration. The reported odds were adjusted for health status, age, and presenting procedure; however, heterogeneity within the categories of each risk factor could have resulted in residual confounding.[40 41] Nonetheless, a component of the increased odds may be related to excessive administration of fluids and fluid overload. A 3.0 kg cat has a blood volume in the order of 170 ml[17] and with few veterinary practices measuring central venous pressure or using fluid pumps to administer i.v. fluids, the potential for volume overload was possible. Careful fluid administration and monitoring should be recommended in cats, though further work is needed to confirm this observation.

The reduction in odds of anaesthetic-related death with pulse and pulse oximetry monitoring during the procedure has not been reported in small animals. Theoretical analyses in human anaesthesia support these findings and have suggested that pulse oximetry would have detected 40–82% of reported perioperative incidents and, when combined with capnography, 88–93%.[42–44] The current work provides further support for the use of pulse oximetry to minimize complications in the intraoperative setting, albeit in another species. Pulse oximetry was not routinely available in veterinary practice at the time of the last UK study,[8] and one could speculate that this now widely adopted monitoring device has contributed to the reduced risk of anaesthetic death reported here. Other methods of monitoring, including capnography, arterial pressure, and electrocardiography, were not retained in the model primarily because they were rarely used (<10% of the controls had these methods), and this study would have had limited power to evaluate them. Nonetheless, the results support the routine monitoring of patient pulse and the use of pulse oximetry during the procedure.

Though there was a trend in the univariable analysis for sedation to be associated with reduced odds compared with general anaesthesia, this association was not significant after adjusting for other variables, particularly health status and intended procedure. Sedation is generally reserved for minor procedures such as diagnostic tests and minor wound repairs, and is more commonly used in lower ASA status cats, and these results would support the suggestion that confounding by health status and procedure was the basis of a perception of reduced risk with sedation compared with anaesthesia. Further, no specific drug or class of drugs was associated with death. Though univariable associations were seen, when adjusted for potential confounders, principally health status, these associations were no longer significant. There were non-significant tendencies (in the multivariable model) to reduced odds with premedication with acepromazine (adjusted OR=0.6, 95% CI 0.3–1.1), benzodiazepines, and opioids combinations (adjusted OR=0.5, 95% CI 0.2–1.4) and similar odds with medetomidine premedication (adjusted OR=1.1, 95% CI 0.3–3.4) compared with no premedication. The lack of increased odds with medetomidine contrasts with strong evidence associating xylazine (another α_2-adrenoceptor agonist) with increased risk in dogs and cats.[3 8] One of the *a priori* hypotheses based on this earlier work was that medetomidine is associated with increased odds of anaesthetic-related death and given the power of the current study to detect major associations, there was no evidence to support this. There were no clear associations with induction or maintenance agents and anaesthetic-related death, suggesting in general that drug-related effects were less important than patient, procedure, and management factors.

In summary, this is the first large-scale prospective study of perioperative mortality in small animals undertaken in the UK for nearly 20 yr. The risk of anaesthetic and sedation-related death has reduced over this time period, but further improvements are required if the risk is to approach that reported in human anaesthesia. Risk factors have been identified that could improve preoperative assessment of cats and help identify those at greatest risk of death; in particular, health status, age, weight, and procedure urgency, and type. Endotracheal intubation may increase the risk of anaesthetic-related death, greater care should be exercised with this procedure and for minor procedures, the provision of oxygen without an endotracheal tube may be more appropriate. Current use of perioperative fluid therapy may be adversely affecting cats and improved monitoring and management of fluid therapy should be considered, including the use of paediatric burette giving sets or infusion pumps to allow careful administration of fluids. Pulse and pulse oximetry monitoring during anaesthesia could reduce complications and should be routinely used.

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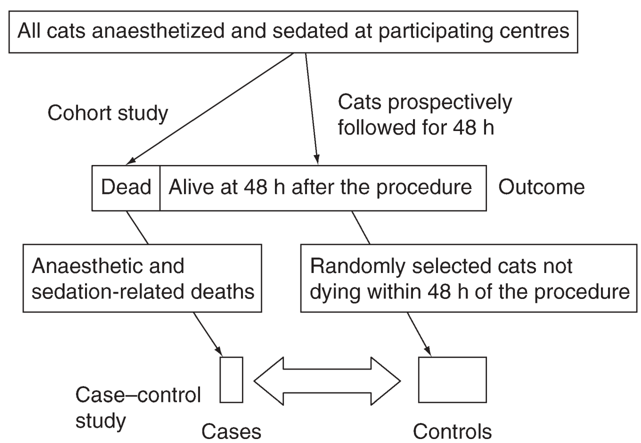
Appendix A

The nested case–control study design: all cats sedated and anaesthetized were followed for 48 h after the procedure and the outcome recorded in the Cohort study. Deaths classified as anaesthetic or sedation-related were defined as cases and compared with randomly selected non-deaths (controls) in the case–control study.



Appendix B

Table B1 Comparison of controls and non-returned controls. *Hauck–Anderson corrected 95% CI for the difference in proportion between the controls and non-returned controls. †Mean and standard deviation are reported and 95% CI for the difference between controls and non-returned controls

Risk factor	Proportion of controls	Proportion of non-returned controls	*P*-value	95% CI* for the difference in proportions
Sedation	55/555 (9.9%)	2/23 (8.7%)	0.84	−15.5 to 13.1%
ASA III–IV	47/555 (8.5%)	3/23 (13.0%)	0.44	−12.0 to 21.1%
Urgent or emergency procedure	97/555 (17.5%)	2/23 (8.7%)	0.27	−23.2 to 5.7%
Major Procedure	35/555 (6.3%)	3/23 (13.0%)	0.20	−9.8 to 23.2%
Age†	5.3 (5.1) yr	4.1 (4.1) yr	0.27	−1.0 to 3.6 yr

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