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Mortality related to general anaesthesia and sedation in dogs under UK primary veterinary care

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Abstract

Objectives To quantify and explore risk factors in dogs seen at primary care UK veterinary clinics for general anaesthetic (GA)/sedative-related death overall, in addition to neuter-specific procedures.

Study design A nested case-control study within UK primary care veterinary electronic patient record surveillance programme, VetCompass, including over 300 UK veterinary practices.

Animals A total of 157,318 dogs undergoing GA/sedative events.

Methods Cases included dogs undergoing GA/sedative events between January 2010 and December 2013 with GA/sedative-related death recorded within 48 hours or 2 weeks of the event. Controls were randomly selected from dogs undergoing GA/sedation that did not die within these time periods. Risks of GA/sedative-related death for all surgeries and neuter-specific surgeries were estimated. Demographic and clinical associations with GA/sedative-related death were reported as odds ratios following multivariable logistic regression modelling. Statistical significance was set at 5%.

Results From 157,318 dogs with a GA/sedative event, there were 159 (0.10%) within 48 hours and 219 (0.14%) GA/sedative-related deaths within 2 weeks. Within 89,852 dogs that underwent a neuter surgery, there were eight GA/sedative related (0.009%). Greater age, poorer American Society of Anaesthesiologists health status scores and more urgent procedures were associated with greater odds of death. Compared with mixed breeds, Rottweilers and West Highland White Terriers had greater odds and Cocker Spaniels had lower odds of GA/sedative-related death.

Conclusions and clinical relevance The overall risk for GA/sedative related death was relatively low, particularly among the subset of dogs undergoing castration or ovariohysterectomy surgery. Associations and risk estimates may assist shared decision-making in clinical practice and provide benchmarks for audit.

Keywords canine, epidemiology, general anaesthesia, mortality, neuter, sedation.

Introduction

In companion animal primary care practice, general anaesthesia (GA) and sedation are undertaken to facilitate a range of procedures from common, noninvasive diagnostics to urgent and highly invasive procedures (Brodbelt et al. 2008a). In humans, the risk of anaesthetic-related death is small, at approximately 0.003%, or three in 100,000 events and so the potential benefits of diagnostic or surgical procedures are often perceived to outweigh this small risk (Bainbridge et al. 2012). In dogs, anaesthetic-related death risks range from 0.05% to 1.29% (Dyson et al. 1998; Gil & Redondo 2013; Itami et al. 2017; Matthews et al. 2017). These higher risks are challenging for owners and veterinarians to weigh when considering elective procedures such as neutering, which may benefit the owner more than the dog, and for which reported estimates of GA/sedative-related risk are sparse.

Identifying factors associated with GA/sedative-related death in dogs would aid the estimation and mitigation of risk by veterinary professionals and owners, allowing better informed decision-making. Risk factors that have been reported in some previous studies have included older age (Brodbelt et al. 2006; Brodbelt et al. 2008b; Gil & Redondo 2013; Bille et al. 2014; Matthews et al. 2017) and poorer health status of the dog, measured using the American Society for Anaesthesiologists (ASA) physical status score (Brodbelt et al. 2008b; Gil & Redondo 2013; Bille et al. 2014; Itami et al. 2017; Smith et al. 2017). In addition, both the urgency of intervention and surgical type have been implicated in the risk of GA/sedative-related death, with more urgent and major surgeries carrying higher risk than minor or scheduled procedures (Brodbelt et al. 2008b; Gil & Redondo 2013; Itami et al. 2017; Matthews et al. 2017). Accurate assessment of risk is needed for a more tailored treatment approach based on characteristics of individual dogs, especially for routine or elective procedures, requiring reliable risk information.

Neuter surgery, including castration or ovariohysterectomy, is a procedure of particular interest for its relationship to GA/sedative-related deaths given its elective nature. Neuter surgeries are recommended for population control (Zawistowski et al. 1998) and potential reductions in undesirable reproductive behaviours (Root Kustritz 2014). However, there is currently concern over anaesthetic risk in early-age neutering (Jupe et al. 2018). Whilst guidelines for anaesthesia of young companion animals exist (Faggella & Aronsohn 1994), there remain concerns over quantifying anaesthetic risks for such routine/elective procedures that are often nonessential to the animal's immediate survival or wellbeing.

The Confidential Enquiry into Perioperative Small Animal Fatalities (CEPSAF) offered the most recent comprehensive report of anaesthetic-related death and its associated risk in the UK (Brodbelt et al. 2008b). This prospective, multicentre study collected data on dogs undergoing anaesthetic or sedative events within 117 UK centres between June 2002 and June 2004. This study employed a manual paper-based survey that recorded specific details of GA/sedative events, including potential risk factors. Within that study period, CEPSAF reported a risk of anaesthetic-related death per event in dogs of 0.15%, with higher risks for dogs that were older, in poorer health status or undergoing urgent or major procedures (Brodbelt et al. 2008b). Larger electronic databases of primary care clinical records have since become available for epidemiological research, which enable more up-to-date and larger investigations (Matthews et al. 2017; Kreisler et al. 2018; VetCompass 2020). An improved evidence base may assist veterinarians in the reduction of overall number of deaths, assist shared decision-making between healthcare professionals and owners for GA/sedative events in clinical practice and provide core benchmarking information for clinical audits (Waine & Brennan 2015).

The current study aimed to quantify, and evaluate risk factors for, GA/sedative-related deaths overall and for neuter-specific procedures in dogs at primary care veterinary practices across the UK.

Materials and methods

Study population

A nested case-control study included dogs in the VetCompass animal surveillance database of anonymized electronic animal records from UK primary care veterinary practices (VetCompass 2020). Data collection for VetCompass began in 2010 and is ongoing, holding clinical, insurance-related and phenotypic information recorded contemporaneously with episodes of care for > 8 million dogs (O'Neill et al. 2014). Ethical approval was granted by the RVC Ethics and Welfare Committee (reference URN 2015 1369). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were used throughout this study (https://www.equator-network.org/reporting-guidelines/strobe/).

The study sample included all dogs that had undergone at least one GA/sedative procedure recorded between 01/01/2010 and 31/12/2013. The final GA/sedative episode for each dog during the study period was included such that each animal contributed only one GA/sedative episode to the study. GA/sedation events were identified using GA and sedative-related search terms (Supporting information). An anaesthetic event required the recorded use, within the veterinary practice, of a general anaesthetic or sedative agent, defined as chemical restraint considered likely to be sufficient/insufficient to allow for endotracheal intubation, respectively. Oral sedatives provided for at-home use were excluded since administration could not be ascertained. The case definition for a GA/sedative-related death required death within 48 hours or 2 weeks of GA/sedation and that the GA/sedative agent could not be reasonably excluded as a contributory factor in the death (GA/sedative death), i.e., deaths not resulting solely from inoperable surgical or pre-existing medical conditions (Brodbelt et al. 2008a). Dogs that underwent a GA/sedative agent purely for euthanasia were excluded. All dogs with key terms relating to death, euthanasia, or cremation (Supporting information) between 01/01/2010 and 14/01/2014 were cross-referenced with dogs recorded as undergoing GA/sedation within the study period. The period for identifying deaths exceeded the study period by 2 weeks to allow for capture of all deaths related to GA/sedative events within the study period. The full clinical records of animals identified as potentially fulfilling inclusion criteria were manually screened to confirm their status for GA/sedative-related death. These were reviewed against the case definition by the primary author (SSW) and a European College of Veterinary Anaesthesia and Analgesia boarded veterinary anaesthetist (JV) and where discrepancies arose, the other authors (DON and DB) adjudicated. Specific causes of death were defined as the final contributory factor considered to have primarily triggered the death (O'Neill et al. 2013).

Control dogs were selected from the remaining dogs that had undergone at least one GA/sedation event between 01/01/2010 and 31/12/2013. Dogs were excluded from the control pool if they had died from GA/sedation-related causes during the study period. Control dogs were not matched to cases in order to explore multiple risk factors for GA/sedation-related death. A random number generator (random.org) was used to identify four unmatched control dogs for each case. The most recent GA/sedative event in each control was extracted.

Risk factor assessment

Clinical and demographic variables embedded automatically within VetCompass were extracted for cases and controls: date of birth, sex, breed, bodyweight and insurance status. Date of birth was used alongside the date of GA/sedation to calculate age at surgery, categorized into ≤ 0.5 years, 0.5−1.5 years, 1.5−3.0 years, 3.0−5.0 years, 5.0−7.0, 7.0−9.0 years, > 9.0 years. Breed was reduced to the 10 most common case and 10 most common control breeds, plus ‘other specific breed’ and a ‘cross-breed’ category, defined as any mixed breed dog, regardless of specific ancestry. In addition, breeds were aggregated to purebreds and cross-breeds and additionally condensed in relation to their brachycephalic status (brachycephalic, mesocephalic and dolichocephalic; Table S1). The most recent bodyweight (before or after) to GA/sedative event within the study period was used for adult dogs (>18 months) and most recent bodyweight within 1 month of GA/sedative events for juveniles (≤18 months).

Additional variables not automatically embedded within VetCompass were manually extracted from the clinical records. These comprised ASA score at GA/sedation [categorized as 1−2, 3 and 4−5, (Brodbelt et al. 2015)] and surgery type [routine/elective, non-routine but scheduled and urgent/emergency, extended from categories previously defined by Brodbelt et al. (2008b)]. Specific primary surgical procedures were categorized: 1) neuter (routine only); 2) dental (all); 3) other noninvasive routine; 4) diagnostic; 5) soft tissue minor; 6) soft tissue major; 7) orthopaedic; and 8) other (Brodbelt 2006) (Table S2). Use of additional imaging or diagnostic investigations (Table S1) secondary to these procedures was also extracted.

For cases, timing of death was recorded relative to the latest anaesthetic protocol: 1) during induction; 2) during maintenance; 3) during reversal; 4) postoperatively on the same day as the procedure; and 5) postoperatively between 1 and 14 days following the procedure. Additionally, cases were split into causes of death: 1) euthanasia; 2) cardiorespiratory; 3) gastrointestinal; 4) neurological; 5) renal; and 6) unclear but not euthanasia.

Outcome assessment

The primary outcome was death related to GA/sedation in the 2 weeks following GA/sedative procedures between 2010 and 2013 and secondary outcomes GA/sedative-related death within 48 hours of these procedures and within 2 weeks of neuter-specific procedures.

Statistical analysis

Data were analysed using StataIC 14 (College Station, TX, US). For variables with ≥ 85% complete data, the primary analysis adopted a complete case analysis. Brachycephalic status could not be assigned to cross-breeds. For variables with < 85% complete data, although these probably had similar missingness mechanisms to the more complete variables, these variables were included only in secondary multivariable models to maintain power for the primary models.

Sample size

The required sample size was estimated at 157−200 cases and 628−800 controls to detect an odds ratio of at least 1.8 for GA/sedative-related death, given between 20% and 50% exposure to a given risk factor in the control arm, 95% confidence level, 90% precision and with a 1:4 case-to-control ratio.

Risk calculations

The risks of GA/sedation-related death following GA/sedation events were estimated by dividing the total number of GA/sedation-related deaths by the number of dogs having undergone at least one GA/sedation event between 01/01/2010 and 31/12/2013. The risk of neuter-specific GA/sedation-related death was calculated by dividing GA/sedative-related deaths within 2 weeks of neuter surgery by all neuter surgeries between 01/01/2010 and 31/12/2013. The 95% confidence intervals (CIs) were constructed using the Clopper-Pearson exact method (Brown et al. 2001).

Risk factors for GA/sedation-related death

Differences in risk factors between cases and controls were assessed initially using univariable logistic regression analyses. Multicollinearity between continuous variables was assessed using Spearman’s correlations. All risk factors were deemed biologically relevant and so all, except for insurance status and bodyweight which had considerable missing data, were forced into multivariable logistic regression modelling for GA/sedative-related death. This primary multivariable model included the breed variable. Secondary models included: 1) the primary model where pure/mixed status replaced breeds; 2) the primary model with brachycephalic status replacing breed; 3) the primary model including bodyweight and insurance status; and 4) the primary model where final variables were included via backwards selection (Table S3). A likelihood ratio test was used to determine whether variables in the full model that were excluded from the backwards stepwise model significantly improved full model fit. Wald tests were used to investigate whether the combination of these variables, and the individual excluded variables themselves, had coefficients equal to zero. In addition, the primary and secondary models were repeated with the outcome limited to GA/sedative-related death within 48 hours. The veterinary practice group was included in all models as a fixed effect in order to account for any confounding effects. Random effects were not used owing to the small number of practice groups (condensed to three for modelling), which would violate the exchangeability assumption of random effects modelling. Practice groups represented over 300 individual practices across the UK and were analysed at the practice group level owing to protocol-driven medicine that may differ between groups. Biologically relevant model pairwise interactions were tested in the final model, with statistical significance set at < 5%. Pearson and Hosmer-Lemeshow tests (10 groups) evaluated overall fit of each model with p values < 0.05 signifying poor fit (Hosmer et al. 2013).

Results

Study population

There were 157,318 dogs that underwent at least one GA/sedative event within VetCompass between 01/01/2010 and 31/12/2013. Of these, 1396 died from all-causes within 2 weeks of the final procedure dates. Therefore, the proportional all-cause risk of death per dog following GA/sedative agents was 0.89% (95% CI: 0.84−0.93%], or 890 in 100,000. Of these 1396, 219 died where anaesthesia could not be reasonably excluded as potential contributor. Therefore, the risk of GA/sedative death within 2 weeks was 0.14% (95% CI: 0.12−0.16%), or 140 in 100,000 and 159 dogs were identified with GA/sedative-related deaths within 48 hours, giving a risk of 0.10% per dog (95% CI: 0.09−0.12%), or 100 in 100,000.

GA/sedative-related risk of death under routine neuter surgery

Of 89,852 dogs that underwent neutering procedures between 01/01/2010 and 31/12/2013, eight had GA/sedative-related deaths within 2 weeks and five within 48 hours. Therefore, the risk of GA/sedative-related death associated with neuter surgery was 0.009% (95% CI: 0.005−0.018%) within 2 weeks, or nine in 100,000, and 0.006% within 48 hours (95% CI: 0.002−0.013%), or six in 100,000. For those that died within 2 weeks of the GA/sedative event, two deaths followed castration and six followed ovariohysterectomy. Of these dogs, five had ASA scores of I or II and three had scores of III. The most recorded cause of death was cardiorespiratory failure [$n =$ 4 (50%)].

All GA/sedative-related deaths

Of those 219 dogs that had GA-sedative-related deaths (cases), 93 (42%) died on the same day as the GA/sedation with the remainder in the following 1 to 14 days. The largest proportions died during anaesthetic maintenance [$n = 44$ (47%)] or postoperatively [$n = 40$ (43%)]. Few died on anaesthetic induction [($n = 7$ (8%)] or reversal [$n = 2$ (2%)]. The primary causes of death were euthanasia after deterioration in health (47%), cardiorespiratory failure (32%) and death outside of the clinical setting (19%) (Table 1). Demographic and clinical data for cases and randomly selected controls ($n = 881$) are presented in Table 2.

Risk factor analysis: GA/sedative-related death within 2 weeks of GA/sedative event

Demographic factors

In the multivariable analysis, older age was associated with increased odds of GA/sedative-related death, with 5.0−7.0 year olds with 4.9 times the odds (95% CI: 1.5−15.6), 7.0−9.0 year olds at 4.9 times the odds (95% CI: 1.7−14.1) and > 9.0 year olds at 12.8 times the odds (95% CI: 4.7−34.9) compared with 0.5−1.5 year olds. Compared with mixed breed dogs, Rottweilers had 8.1 times the odds (95% CI: 1.3−49.5), West Highland White Terriers 5.4 times the odds (95% CI: 1.1−27.2) and Cocker Spaniels 0.1 times the odds (95% CI < 0.1−0.7) of GA/sedative-related death. Compared with mesocephalic breeds, dolichocephalic dogs had 3.7 times the odds of GA/sedative-related death (95% CI: 1.7−8.3). There was no significant difference between mesocephalic and brachycephalic breeds in terms of GA/sedative-related death and neither sex nor insurance status was associated with this outcome (Table 2, Fig. 1a and b, Tables S5 & S6).

Clinical factors

In the multivariable analysis, compared with dogs with an ASA score of I or II at the time of GA/sedation, dogs with an ASA score of III had 4.8 times the odds of GA/sedative-related death (95% CI: 2.3−10.1) and those with ASA IV-V had 19.0 times the odds (95% CI: 7.1−50.8). Urgent/emergency surgeries were associated with 13.6 times the odds (95% CI: 2.2−84.5) of GA/sedative-related death compared with routine or elective. The specific surgery types did not differ in odds of GA/sedative-related death (Table 2, Fig. 1c).

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Table 1 Causes of death in dogs that suffered a general anaesthesia (GA)/sedative-related death identified in VetCompass between 2010 and 2013 from a total of 157,318 dogs undergoing GA/sedative events

Cause of death	Anaesthetic-related mortality, number of dogs (%)
Euthanasia	102 (47)
Cardiorespiratory	69 (32)
Gastrointestinal	2 (1)
Neurological	2 (1)
Renal	1 (<1)
Died outside of clinical setting without specific cause of death noted	42 (19)
Total	**219 (100)**

Secondary analysis: backwards stepwise modelling

In secondary analyses, a model constructed using backwards stepwise variable selection identified a fewer number of variables associated with GA/sedative-related death (Table S3). A likelihood ratio test demonstrated improved fit of the more comprehensive model ($p < 0.001$, χ^2: 144.8, df: 11) compared with the final reduced model (Table S3). Wald tests demonstrated that urgency of procedure ($p = 0.017$), age ($p < 0.001$), ASA status ($p < 0.001$) and breed ($p = 0.018$) significantly added to the model, as well as brachycephalic status ($p = 0.003$) when this was interchanged with full breed list. All multivariable models, including this secondary model demonstrated good model fit ($p > 0.05$) according to Pearson and Hosmer-Lemeshow tests.

Risk factor analysis: anaesthetic-related death within 48 hours of anaesthetic event

The associations identified for GA/sedative-related death within 2 weeks were similar to those within 48 hours post-GA/sedative event although there were some differences in breed associations (Table S4). In addition, compared with diagnostic procedures, dental procedures were associated with 8.5 times the odds (95% CI: 1.2−61.0) of 48 hour GA/sedative-related death. In contrast, compared with diagnostic procedures, minor soft tissue procedures had 0.3 times the odds (95% CI: 0.1−0.8) of 48 hour GA/sedative-related death (Table S4).

Discussion

In over 150,000 dogs undergoing at least one GA/sedation event between 2010 and 2013, the risk of GA/sedative-related death was approximately 0.10−0.14%. This risk was lower for routine and elective procedures, with that from routine neuter surgery at 0.009%, or nine in every 100,000 dogs neutered. Factors associated with increased risk of GA/sedative-related death included older age, specific breeds, poorer health status at the time of GA/sedation and greater procedural urgency. These factors should be weighed against the benefits of GA/sedation when considering anaesthetic interventions.

The risk of GA/sedative-related death for dogs followed between 2010 and 2013 was 0.10% within 48 hours and 0.14% within 2 weeks of the procedure. The current study estimated the risk of death per dog over the study period and is therefore not entirely comparable to CEPSAF. CEPSAF, the most recent prospective multicentre UK study (2002−2004), reported 0.17%, using the risk of death per GA/sedative event, rather than per dog (Brodbelt et al. 2008a,b). If one GA/sedative event per dog is assumed, then the estimate from the current study is less than that from CEPSAF a decade previously. If there were more than one event per dog, the current estimate would be further reduced. This may be owing to a combination of the study populations, which for CEPSAF, like the current study, was primarily primary care, but also included secondary care data and a potential reduction in risk over time.

A broad case definition of GA/sedative-related deaths was employed in the current study, further suggesting a reduction in the rate of GA/sedation-related deaths over time. Our definition extended to 2 weeks following a GA/sedative event. This allowed inclusion of euthanasia and deaths that occurred outside the clinic as final causes of death if anaesthesia could not be excluded as a contributing factor. In the current study, within the small number of dogs that had GA/sedative-related death associated with neuter surgeries, five of eight died within 48 hours (63%), suggesting this is a critical period for careful observation during and following neuter surgeries. However, for overall GA/sedative-related deaths across different procedures, 58% of deaths occurred at least 1 day after the GA/sedative, corroborating evidence from a collection of single-centre studies (Hosgood & Scholl 2007; Robinson et al. 2014; Levy et al. 2017). In multicentre studies, 77% of deaths occurred postoperatively across 39 Spanish clinics (Gil &Redondo 2013) and in 82% of dogs across 18 Japanese referral hospital (Itami et al. 2017). This was despite deaths occurring in less than half of dogs postoperatively in the CEPSAF study (Brodbelt et al. 2008a). Previous suggestions of closer monitoring following anaesthetic events (Brodbelt et al. 2008a) may have proven beneficial in mitigating GA/sedative-related death. Further, when the current analysis limited the window for GA/sedative-related deaths to 48 hours post procedure, the risk of anaesthetic-related death decreased to 0.10%, with an upper 95% confidence estimate (0.12%) less than that of CEPSAF. Therefore, even when deaths that occurred outside the clinical setting were included, using the same period, GA/sedative-related deaths in the UK may have decreased between 2000 and 2013, assuming similar caseloads in terms of overall animal health and procedures.

Table 2 Risk factors for GA/sedative-related death within 2 weeks of GA/sedative between 2010 and 2013 in dogs under primary veterinary care within VetCompass using univariable and multivariable analyses ($n = 1100$)

Variable	% Data available	*N* (%) or median (IQR)		Univariable			Multivariable		
		Case ($n = 219$)	Control ($n = 881$)	OR	95% CI	*p* value	OR	95% CI	*p* value
Demographic									
Age at GA/sedation (years)	99								
≤ 0.5		6 (3)	54 (6)	2.7	1.0–7.4	0.053	4.1	1.0–17.0	0.064
0.5–1.5		13 (6)	317 (36)	Reference	Reference	Reference	Reference	Reference	Reference
1.5–3		7 (3)	119 (14)	1.4	0.6–3.7	0.453	1.0	0.3–3.9	0.983
3–5		19 (9)	123 (14)	**3.8**	**1.8–7.9**	**< 0.001**	2.1	0.7–3.9	0.106
5–7		23 (11)	75 (9)	**7.5**	**3.6–15.4**	**< 0.001**	**4.9**	**1.5–15.6**	**0.009**
7–9		38 (17)	77 (9)	**12.0**	**6.1–23.7**	**< 0.001**	**4.9**	**1.7–14.1**	**0.003**
> 9		112 (51)	105 (12)	**26.0**	**14.1–48.1**	**< 0.001**	**12.8**	**4.7–34.9**	**< 0.001**
Sex	100								
Male		109 (50)	443 (50)	Reference	Reference	Reference	Reference	Reference	Reference
Female		110 (50)	438 (50)	1.0	0.7–1.4	0.928	1.3	0.7–2.2	0.443
Breed*	100								
Mixed breed		35 (16)	183 (21)	Reference	Reference	Reference	Reference	Reference	Reference
Bichon Frise		3 (1)	18 (2)	0.9	0.2–3.1	0.832	1.5	0.2–10.2	0.763
Border Collie		6 (3)	33 (4)	1.0	0.4–2.4	0.916	0.3	0.1–1.1	0.069
Cavalier King Charles Spaniel		7 (3)	19 (2)	1.9	0.8–4.9	0.171	3.1	0.6–15.1	0.165
Chihuahua		3 (1)	27 (3)	0.6	0.2–2.0	0.393	1.0	0.2–5.6	0.917
Cocker Spaniel		4 (2)	43 (5)	0.5	0.2–1.4	0.194	**0.1**	**< 0.1–0.7**	**0.025**
German Shepherd Dog		17 (8)	15 (2)	**5.9**	**2.7–13.0**	**< 0.001**	2.6	0.5–12.3	0.251
Golden Retriever		6 (3)	13 (1)	2.4	0.9–6.8	0.095	0.7	0.1–3.4	0.320
Jack Russell Terrier		6 (3)	52 (6)	0.6	0.2–1.5	0.281	0.3	0.1–1.5	0.118
Labrador Retriever		16 (7)	80 (9)	1.0	0.5–2.0	0.892	1.7	0.6–5.0	0.320
Rottweiler		6 (3)	9 (1)	**3.5**	**1.2–10.4**	**0.025**	**8.1**	**1.3–49.5**	**0.026**
Shih Tzu		4 (2)	31 (4)	0.7	0.2–2.0	0.484	1.0	0.1–6.5	0.964
Springer Spaniel		6 (3)	20 (2)	1.6	0.6–4.2	0.369	2.2	0.4–13.5	0.457
Staffordshire Bull Terrier		13 (6)	62 (7)	1.1	0.5–2.2	0.796	1.0	0.3–3.2	0.966
West Highland White Terrier		13 (6)	15 (2)	**4.5**	**2.0–10.4**	**< 0.001**	**5.4**	**1.1–27.2**	**0.011**
Yorkshire Terrier		3 (1)	3 (5)	0.5	0.1–1.7	0.281	0.8	0.1–4.2	0.717
Other pure breed		71 (32)	230 (26)	**1.6**	**1.0–2.5**	**0.026**	1.7	0.7–3.9	0.156
Clinical									
ASA score at GA/ sedation	99								
I–II		34 (16)	749 (86)	Reference	Reference	Reference	Reference	Reference	Reference
III		93 (43)	92 (11)	**22.3**	**14.2–34.9**	**< 0.001**	**4.8**	**2.3–10.1**	**< 0.001**
IV–V		91 (42)	28 (3)	**71.6**	**41.5–123.5**	**< 0.001**	**19.0**	**7.1–50.8**	**< 0.001**
Urgency of GA/sedation	99								
Routine/elective		11 (5)	518 (59)	Reference	Reference	Reference	Reference	Reference	Reference
Non-routine scheduled		51 (23)	240 (27)	**10.0**	**5.1–19.5**	**< 0.001**	**6.9**	**1.3–37.5**	**0.015**
Urgent/emergency		157 (72)	117 (13)	**63.2**	**33.2–120.2**	**< 0.001**	**17.0**	**2.7–105.9**	**< 0.001**
Primary surgery type	100								
Diagnostic		78 (36)	122 (14)	Reference	Reference	Reference	Reference	Reference	Reference
Dental (all)		8 (4)	64 (7)	**0.2**	**0.1–0.4**	**< 0.001**	4.8	0.9–24.8	0.069
Neuter (routine only)		8 (4)	454 (52)	**< 0.1**	**< 0.1–0.1**	**< 0.001**	4.1	0.7–25.9	0.167
Noninvasive routine		5 (2)	11 (1)	0.7	0.2–2.1	0.541	7.3	0.8–66.4	0.085
Orthopaedic		7 (3)	13 (1)	0.8	0.3–2.2	0.726	1.9	0.4–8.0	0.405
Soft tissue minor		19 (9)	158 (18)	**0.2**	**0.1–0.3**	**< 0.001**	0.6	0.2–1.3	0.278
Soft tissue major		90 (41)	50 (6)	**2.8**	**1.8–4.4**	**< 0.001**	1.6	0.8–3.3	0.179
Other		4 (2)	7 (1)	0.8	0.3–3.2	0.861	0.5	0.1–4.5	0.546

Table 2 (*continued*)

Variable	% Data available	*N* (%) or median (IQR)		Univariable			Multivariable		
		Case ($n = 219$)	Control ($n = 881$)	OR	95% CI	*p* value	OR	95% CI	*p* value
Additional secondary investigations	99	161 (74)	306 (35)	**5.1**	**3.7–7.2**	**< 0.001**	1.6	0.9–2.9	0.081
Practice type*									
Group 1	100	51 (23)	155 (18)	Reference	Reference	Reference	Reference	Reference	Reference
Group 2		164 (75)	236 (27)	**2.1**	**1.5–3.1**	**< 0.001**	0.8	0.4–1.4	0.402
Group 3		4 (2)	490 (56)	**< 0.1**	**< 0.1–0.1**	**< 0.001**	**<0.1**	**< 0.1–< 0.1**	**< 0.001**

ASA, American Society of Anesthesiologists physical status score; CI, confidence interval; GA, general anaesthetic; IQR, interquartile range; OR, odds ratio. *Additional secondary model included all covariates (breed) plus bodyweight and insurance status. All risk factor OR (95% CI) described where full breed in model. Practice type names are not reported for interpretability and data protection reasons.

Both the urgency and nature of procedures requiring anaesthesia have been previously implicated in GA/sedative-related deaths. Major surgeries remained associated with anaesthetic-related death in the previous CEFSAF study after adjusting for the urgency of procedure, ASA status and age (Brodbelt et al. 2008b). However, the current study did not show differences between surgical types compared with diagnostic procedures in the multivariable analyses. On the other hand, urgent or emergency procedures were associated with 17 times the odds of GA/sedative-related death within 2 weeks and 57 times the odds within 48 hours compared with routine or elective procedures. More urgent procedures have been associated with increased risk of anaesthetic death in 237 dogs across 822 American hospitals (Matthews et al. 2017) and increased odds in CEPSAF (Brodbelt et al. 2008b). In the present study, surgical type was no longer associated with GA/sedative-related death once procedure urgency was accounted for. This finding suggests that differing GA/sedation durations, and the difficulty and invasiveness of surgery, may play lesser roles in anaesthetic safety than the physical condition of the dog at presentation. Likewise, the large association between insurance status and GA/sedative-related death, which reduces after multivariable adjustment, is also probably a reflection of surgical urgency, as well as the nature of procedures undertaken. Owners that insured their dogs may be more willing and able to afford urgent, and potentially more major, veterinary procedures (Egenvall et al. 2009). The increased associations of urgency and attenuation of associations for procedure type between CEPSAF and the current study may suggest an improvement in modifiable surgical factors over the past decade that have previously associated with anaesthetic-safety incidents. These include the use of new technologies, healthcare professional proficiencies, work environment and/or surgical management (McMillan & Lehnus 2018), leaving the unmodifiable condition at presentation and urgency the core element associated with GA/sedative-related death. Poorer ASA status is frequently associated with higher odds of GA/sedative-related death across cohorts nationally and internationally (Brodbelt et al. 2006, 2008b; Gil & Redondo 2013; Bille et al. 2014; Itami et al. 2017; Smith et al. 2017). ASA physical status score remains of paramount importance when understanding and predicting risks of anaesthesia.

Independent of health status, individual breeds are associated with specific health predispositions that may affect their risk of anaesthesia-related death. Compared with mixed breed dogs, West Highland White Terriers and German Shepherds had increased risks of anaesthetic-related death within 48 hours of the procedure, even after taking health status and procedural urgency into account. These two breeds were also associated with anaesthetic-related death in CEPSAF (Brodbelt et al. 2008b), alongside Cocker Spaniels which were associated with lower odds of GA/sedative-related death in the current study. The present study additionally identified Rottweilers at particularly increased odds of GA/sedative-related death within 2 weeks of the GA/sedative event compared with mixed breed dogs. Dolichocephalic breeds had increased odds of GA/sedative-related death within both 48 hours and 2 weeks compared with mesocephalic breeds, with no difference in risk for brachycephalic breeds. Brachycephaly has previously been associated with increased odds of anaesthetic complications (Gruenheid et al. 2018). Given the welfare concerns for brachycephalic dogs, specifically conditions such as brachycephalic obstructive airway syndrome (Downing & Gibson 2018), brachycephaly was expected to be associated with increased risks of GA/sedative-related death. The lack of association in the current study, paired with increased odds of GA/sedative related death in dolichocephalic dogs, suggests either an additional risk pathway specific to dolichocephalic dogs or increased vigilance during anaesthesia, or reluctance to administer anaesthetic agents, in the presence of brachycephaly. In either instance, it appears that dolichocephalic dogs may require additional attention during GA/sedation.

Greater age was associated with increased odds of GA/sedative-related death within 48 hours and 2 weeks. This association has not been shown consistently in previous studies and cut-points have tended to restrict the comparison to

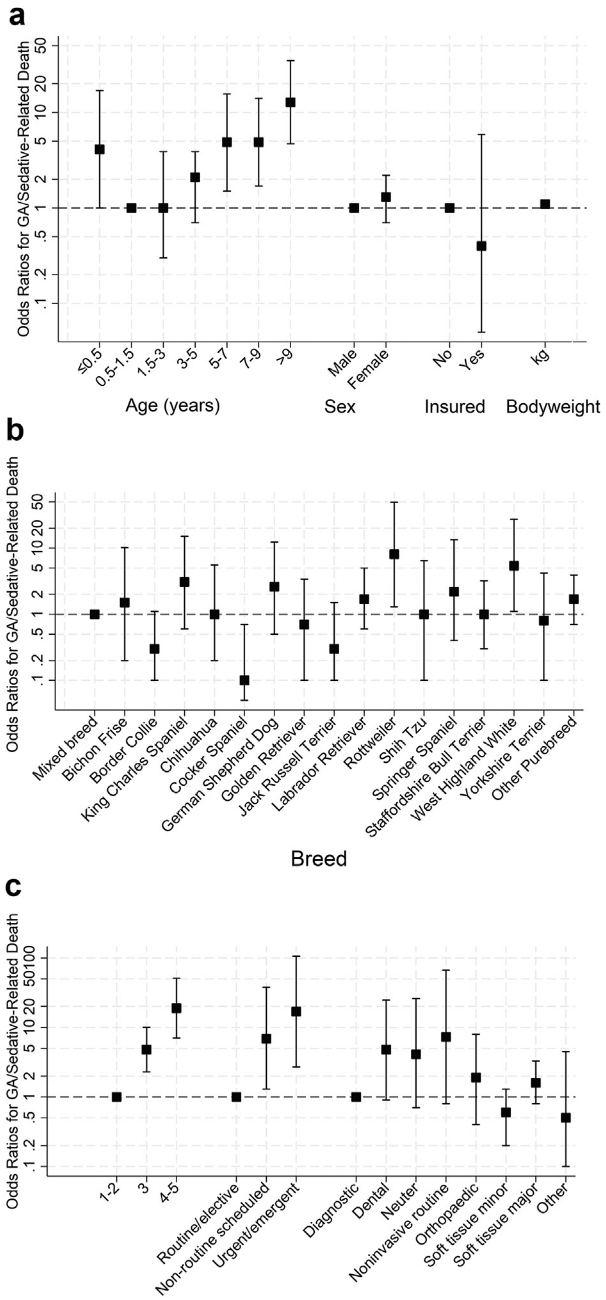

Figure 1 Multivariable associations with general anaesthesia (GA)/sedative-related death within 2 weeks of GA/sedative between 2010 and 2013 in dogs under primary veterinary care within VetCompass: (a) Demographic. (b) Breed. (c) Clinical. Squares represent odds ratio point estimates with the bars represent 95% confidence intervals.

geriatric *versus* non-geriatric dogs, with geriatric dogs having increased odds of anaesthetic-related death (Brodbelt et al. 2008b; Gil & Redondo 2013; Bille et al. 2014). In the current study, eight deaths were noted for neuter surgeries, with affected dogs ranging from 6 months to 9 years of age. No statistically significant difference in the odds of GA/sedative-related death was evident between puppies < 6 months of age and those between 6 and 18 months.

Limitations of the current study relate to potential over-estimation of GA/sedative-related death risk and potential misclassifications of both cause of death and risk factor data. Rarely did clinical notes clearly denote 'GA/sedative-related death' and this outcome was inferred from the cause of death and clinical notes. It is possible that further detailed postmortem examination/necropsy may have ruled out a proportion of dogs deemed to be cases in the current study. However, the current study used an independent assessor to improve the consistency of classification. Conversely, the unfeasibility of blinding the study investigators to case and control assignment may have resulted in misclassification of subjectively scored risk factors, such as ASA status score. In addition, since multiple breeds with small sample sizes were included in the risk factor analyses, the results reported for breed-specific odds ratios should be interpreted with caution, particularly for those with wide CIs. Controls were randomly matched to cases and so there was an uneven distribution across practice groups. While certain practice groups may have overrepresented control dogs, in multivariable models this variable was statistically adjusted for to minimize bias from different veterinary protocols. Finally, certain risk factors such as specific anaesthetic/sedative agents, GA *versus* sedative risks, timing of procedures and staffing could not be explored for the associations with GA/sedative-related death. Often, specific surgical procedures rather than GA/sedative drugs were listed within electronic medical records, while procedural and staffing note-taking differed considerably between practices and veterinarians. These factors could therefore not be explored in the current study.

Conclusions

In over 150,000 dogs across the UK, risk of GA/sedative-related death was 0.14%. Neuter surgery had a low risk (0.009%) of death. Dogs at higher risk were older, in poorer heath or underwent more urgent procedures. Rottweilers and West Highland White Terriers had higher risk, whereas Cocker Spaniels were protected. These estimates may aid in shared decision-making on GA/sedation risk, as well as provide benchmarks for clinical audits.

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Authors' contributions

SSW: study design, analysis and interpretation of data, preparation and final approval of the manuscript. DON: study design, acquisition and interpretation of data, preparation and final approval of the manuscript. JV: analysis and interpretation of data, preparation and final approval of the manuscript. DB: study design, acquisition and interpretation of data, preparation and final approval of the manuscript.

Conflict of interest statement

The authors declare no conflict of interest.

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Supporting Information.

Additional Supporting Information may be found in the online version of this article: https://doi.org/10.1016/j.vaa.2022.03.006.

Table S1: Specific procedure assignment within procedure categories for dogs undergoing a GA/sedative event and followed in the VetCompass Animal Surveillance database between 2010 and 2013.

Table S2: Specific breeds categorized by brachycephalic status for dogs undergoing a GA/sedative event and followed in the VetCompass Animal Surveillance database between 2010 and 2013.

Table S3: Risk factors for GA/sedative related death with 2 weeks of procedure using a multivariable, backwards-stepwise built logistic regression model.

Table S4: Risk factors for GA-sedative-related death within 48 hours of GA/sedative between 2010 and 2013 in dogs under primary veterinary care within VetCompass in univariable and multivariable analyses ($n = 1040$).

Table S5: Additional breed categorizations and their associations with GA/sedation-related death within 2 weeks of GA/sedative between 2010 and 2013 in dogs under primary veterinary care within VetCompass in univariable and multivariable analyses ($n = 1040$).

Table S6: Additional variables with fewer complete data and their associations with GA/sedation-related death within 2 weeks of GA/sedative between 2010 and 2013 in dogs under primary veterinary care within VetCompass in univariable and multivariable analyses ($n = 1040$).

