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AUTHORS: H.W. Lee, H. Machin, C. Adami

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Peri-anaesthetic mortality and non-fatal gastrointestinal complications in pet rabbits: a retrospective study on 210 cases

H.W. Lee[a], H. Machin[a], C. Adami[a]*

[a]*Department of Clinical Sciences and Services, Royal Veterinary College, University of London, AL97TA, North Mymms, Hatfield, Hertfordshire, UK*

***Corresponding author**

e-mail address: c.adami@rvc.ac.uk; Tel: +44 (0)1707 6629

Other authors' e-mail addresses:

Hoi Wun Lee: *hlee2@rvc.ac.uk*

Hanna Machin*: hmachin@rvc.ac.uk*

Chiara Adami*: c.adami@rvc.ac.uk*

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Authors' contributions

HWL: data collection, statistical analysis, data interpretation and preparation of manuscript;

CA: Study design, preparation and critical revision of the manuscript RG;

HM: Contribution to the study design and to results interpretation, critical revision of the manuscript.

Conflict of interest statement

The authors declare no conflicts of interests.

Original study

Abstract

Objectives The aim of this study was to determine the incidence and the associated risk factors of perianaesthetic mortality and gastrointestinal complications in pet rabbits.

Study design Retrospective cohort study.

Animals A total of 210 pet rabbits admitted to the Exotic Referal Service of Beaumont Sainsbury's Animal Hospital (BSAH) over the period 2009-2016.

Methods The clinical records of the rabbits were obtained from the database. In order to evaluate the incidence of perianaesthetic mortality, three possible outcomes were considered: alive, dead or euthanized within the 72 hours following the anaesthetic event. Food intake and stool production during the first 72 hours following the anaesthetic event were evaluated to investigate the occurrence of gastrointestinal complications. Thereafter, various hypothesised risk factors, including administration of alpha-2 agonists, body weight, American Society of Anesthesiologist classification and endotracheal intubation were tested against perianaesthetic mortality and gastrointestinal complications, with both univariate and multivariate binary logistic regression.

Results Twenty-five out of 185 rabbits underwent two anaesthetic events, therefore data from 210 cases were used. Of the 185 rabbits which had been anaesthetized once, six died during sedation or general anaesthesia and four (one of which euthanized) died during the first 72 postoperative hours, accounting for an actual mortality rate equal to 18.5% (95% confidence interval: 0.025 - 0.086). Perianaesthetic gastrointestinal complications developed in 77 (38%) out of the 204 anaesthetic events whose outcome was not death (95% confidence interval: 0.314 to 0.446). Species-specific risk factors could not be identified for perianaesthetic mortality; however the odds for post-anaesthetic gastrointestinal complications increased significantly with body weight (p=0.01).

Conclusions and clinical relevance Our findings confirm that rabbits continue to have a higher incidence of perianaesthetic mortality than dogs and cats, and highlight a high risk for non-fatal perianaesthetic gastrointestinal complications in this species.

Keywords anaesthesia, gastrointestinal complications, peri-anaesthetic mortality, pet rabbit, *Oryctolagus cuniculus*

Introduction

In the United Kingdom, European domestic rabbits (*Oryctolagus cuniculus*) are becoming increasingly popular as companion animals, which implies a greater demand for rabbit anaesthesia compared to the past. Rabbits are commonly anaesthetized to undergo surgery and other invasive procedures (Wenger 2012), while sedation is often required to allow diagnostics, including oral examination, dental radiographic study and trimming (Hillyer 1994).

Owing to anatomical, physiological, and behavioural features, rabbits carry a higher risk of anaesthesia-related death and gastrointestinal complications than other domestic species (Orr et al. 2005; Brodbelt et al. 2008; Cooper et al. 2009; Leach et al. 2009). The peculiar anatomy of the oropharynx, together with the long incisors and the well-developed masticatory muscles, limits the visibility of the rima glottidis, thus increasing the technical difficulty of orotracheal intubation (Johnson-Delaney & Orosz SE 2011). Additionally, rabbits are prone to develop laryngeal spasm as a sequel of mechanical stimulation; as a result, attempting to intubate the trachea of an inadequately anaesthetized rabbit is likely to cause laryngeal damage (Fick & Schalm 1987).

With respect to the behavioural peculiarities, as prey animals, rabbits are reluctant to show signs of disease (Heard 1993), which can make early detection of even severe clinical conditions extraordinarily challenging. This may cause an underestimation of the real

anaesthetic risk. Bacterial pneumonia accompanied by pneumonic abscessation and pulmonary metastatic adenocarcinoma are relatively common in rabbits, and although these conditions may be subclinical and often remain undetected despite accurate thoracic auscultation, they can lead to chronic respiratory compromise (Hillyer 1994).

The choice of the anaesthetic protocol may also affect the outcome, with some agents causing more adverse effects than others. Various drug combinations has been described for use in rabbits, none of which have clearly identified risk factors associated with mortality (Borkowski & Karas 1999; Henke et al. 2005; Hillyer 1994; Wenger 2012). However, one study found that rabbits anaesthetized with medetomidine-based drug combinations were more prone to develop laryngospasm and bradycardia (Grint & Murison 2008).

The primary aim of this study was to investigate the incidence of perianaesthetic mortality and non-fatal gastrointestinal complications in the study population. The second aim was to determine whether type of anaesthetic event and clinical procedure, administration of alpha-2 agonists, endotracheal intubation, age, body weight and American Society of Anesthesiologists physical status (ASA) classification of the rabbits represented risk factors associated with perianaesthetic mortality and gastrointestinal complications.

Our hypotheses were that administration of alpha-2 agonists as part of the anaesthetic protocol, intubation of the trachea and general anaesthesia (GA) *versus* sedation would be risk factors associated with perianaesthetic mortality, and that abdominal surgeries and administration of alpha-2 agonists would increase the incidence of perianaesthetic gastrointestinal complications.

Materials and Methods

The study was designed as a retrospective cohort study, and performed under permission of the Clinical Research Ethical Review Board of the Royal Veterinary College (License number: 2016/U100).

Data were obtained from the files of pet rabbits admitted to the Exotic Referal Service of Beaumont Sainsbury's Animal Hospital (BSAH) during the period 2009-2016. At the BSAH it is common practice to schedule post-intervention appointments 3 days after the procedure, which allowed for a 72-hour follow up for all rabbits enrolled in the study.

Multiple key words were entered in the VetCompass database to finalize the search of all possible anaesthetics and sedations within the clinical records: "rabbit castration/neutering/spay", "rabbit anaesthetic/anaesthesia/GA", "rabbit sedation", "rabbit CT", "rabbit dental", "rabbit surgery" and "rabbit procedure". Animals which were sedated to be euthanized, or euthanized during the procedure owing to poor prognosis, were excluded from the study.

"Anaesthetic death" was defined as any death occurring within 72 hours after sedation or GA, when no other causes of death could be identified.

Any of the following events recorded within 72 hours from sedation or GA, reported either by the owner (for non-hospitalized animals) or by the nurse in charge (for hospitalized animals), was considered a perioperative gastrointestinal complication: decreased food intake, decreased or increased faecal output, and diarrhoea. The need for syringe-feeding, decided by the clinician on the basis of decreased appetite in the postoperative period, also fell into this definition.

The search was manually refined in order to exclude the files of rabbits that were admitted to the hospital but did not undergo sedation or GA. For each selected file, the following variables were recorded on an Excel sheet (Microsoft Excel 2007): breed, age (in years), sex,

body weight (in kg), ASA classification, type of intervention, anaesthetic protocol, type of anaesthetic event (sedation or general anaesthesia) and endotracheal intubation (yes or no). With respect to the latter, unsuccesful attempts to intubate the trachea were still categorized as "yes". The ASA classification risk was retrospectively assigned by the authors based on clinical history, results of the preanaesthetic physical exam and, when available, blood results of the rabbits.

For the purpose of statistical anaylisis, variables with more than two possible outcomes were categorized as follows. The anaesthetic event was defined as either "sedation" or "general anaesthesia" on the basis of how the event was classified by the anaesthesist in charge, as reported on the anaesthetic record. When this information was not available, the anaesthetic event was classified retrospectively, based on the data extrapolated from the clinical records and billing information. If the anaesthetic protocol included either an injectable induction agent administered IV, including ketamine (Narketan; Vetoquinol, France), propofol (PropoFlo; Abbot, UK), and alfaxalone (Alfaxan; Jurox, Australia) or/and an inhalational agent, then the anaesthetic event was classifed as "GA". All the other drug combinations used fell into the category "sedation".

The interventions classified as "minor procedures" included were: blood sampling, diagnostic imaging, endoscopy, wound cleaning/dressing change, tear duct flush, routine dental filing, "non-abdominal surgeries" (ear surgeries, rhinotomy, lumpectomy and male castration) or "abdominal surgeries" (spaying, cystotomy and exploratory laparotomy). Regarding the anaesthetic protocol, the two possible outcomes were "alpha-2 agonists-based protocols", and "protocols without alpha-2 agonists". When rabbits underwent more than one general anaesthetic, the second anaesthetic event was excluded from data analysis. However, rabbits undergoing sedation followed by general anaesthesia with more than two months apart were included twice, and each anaesthetic event was considered a stand-alone case.

Statistical analysis

Commercially available software was used for statistical analysis (IBM SPSS Statistics 22.0, NV, United States). Missing value analysis was run to a descriptive level to identify extreme data points of the population. Following, the distribution of continuous variables was assessed with Skewness and Kurtosis tests for normality.

Univariate binary logistic regression, run separately for each variable, was used to determine whether type of procedure, anaesthetic protocol, age, sex, breed, body weight, ASA classification and endotracheal intubation were risk factors for perianaesthetic death and gastrointestinal complications. With respect to the variable "body weight", only data from rabbits aged more than 6 months and small breeds rabbits of comparable body size (Dutch, Dwarfs, Dwarf-Lop, Lionhead, Lop, Mini, Himalayan, Tan and Rex) were used for statistical analysis; this accounted for a total of 112 subjects. When the univariate binary logistic regression showed a significant result, a multivariable binary logistic regression model was applied. Manual forward selection was used to construct the regression model. In order to examine variables that were found significant risk factors in the univariate but not in the multivariate model, and also to investigate correlations between variables, Spearman's and Chi-square tests were performed where appropriate. The level of significance was defined as a p-value <0.05.

Results

Study population

The preliminary search identified files from 1171 pet rabbits, only 185 of which had been sedated or anaesthetized at the hospital. These were shortlisted and included in the study. A total of 57% of the rabbits (n=125) were male. None of the variables was normally

distributed. The medians and interquartile ranges for age and body weight of all 185 rabbits were 1.8 0.6 – 4.1] years and 1.9 1.5 – 2.4] kg, respectively. The Skewness and Kurtosis normality tests showed a moderate level of asymmetry in age distribution within the study population, with values of 1.012 and 0.079, respectively, while the level of asymmetry was found severe with respect to the body weight of the rabbits (Skewness value = 1.310; Kurtosis value = 2.329). There was no correlation between body weight and age (p=0.246) and gender (p=0.053). Twenty-four different breeds were represented (Table 1).

Anaesthesia

Of the 185 rabbits, 13% (n=25) underwent two anaesthetic events (one sedation and one general anaesthesia); hence, data from 210 anaesthetic events were used for statistical analysis. Of the 210 anaesthetic events, only 15% of the cases (n=32) were sedations, whereas the majority (85%; n=178) were GA. This information was obtained directly from the anaesthetic record (as classified by the anaesthesist) in 94% of the cases (n=197), and retrospectively extrapolated in the remaining 6% (n=13). A preanaesthetic examination was performed in all rabbits by an anaesthesist. With respect to the ASA classification, a grade 1 was assigned in 57.6% (n=121) of the cases, while grades 2, 3 and 4 were assigned to the 40%, the 1.4% and the 0.95% (n=84, 3 and 2 out of 210 cases, respectively). Endotracheal intubation was either successfully performed or attempted in 37% (n=78) of the cases. The decision whether rabbits should have had their tracheas intubated was clinician-dependent and the selected intubation technique was not reported. Perioperative fluid therapy was administered in 49% (n=102) of the cases, with great variability in terms of choices of fluid type (Lactated Ringer's solution, NaCl 0.9% or Glucose 2.5%), rate (5-10 mL kg hour^{-1} when specified) and route of administration (IV or SC). In 70% (n=148) anaesthetic events, the anaesthetic protocol was based on an alpha-2 agonist (medetomidine, Sedastart; Animalcare, UK), either alone or in combination with other agents. In all cases medetomidine was

170 administered IM (dose range: 0.07-0.15 mg kg^{-1}). Other drugs, used in combination with
171 either medetomidine or other agents to provide sedation/premedication, were fentanyl
172 (Fentadon; Dechra, UK; n=19), buprenorphine (Vetergesic; VioVet, UK; n=96); morphine
173 (Morphine Sulfate; Hameln Pharmaceuticals, UK; n=1), butorphanol (Torphasol; AniMedica
174 GmbH, UK; n=75), midazolam (Dormicum; Roche, Switzerland; n=36), and acepromazine
175 (ACP injectable; Novartis, Switzerland; n=1). In most of the cases, when ketamine was used
176 it was administered IM in combination with medetomidine (n=129), and only in 4 rabbits this
177 agent was administered IV for induction of general anaesthesia. Alfaxalone was administered
178 in 16 rabbits, 9 of which received it IM to achieve a deep sedation, while the other 7 IV as an
179 induction agent. Propofol was administered IV to 4 rabbits to induce anaesthesia. Inhalational
180 anaesthesia, based on either isoflurane (Isoflurane; VetOne, UK) or sevoflurane (SevoFlo;
181 Abbott, UK) in oxygen, was delivered to 56 rabbits, via either face or laryngeal mask, or
182 endotracheal tube. A perioperative analgesia combination of a NSAID - either meloxicam
183 (Metacam; Boehringer Ingelheim, Canada) or carprofen (Rimadyl; Pfizer, UK) - and an
184 opioid was administered to each rabbit undergoing invasive procedures. Monitoring, when
185 reported, consisted of both clinical (detection of pulse rate, evaluation of chest excursion to
186 detect the respiratory rate, and evaluation of palpebral and corneal reflexes) and instrumental
187 monitoring. The latter was based on pulse oximetry - with or without a Doppler blood flow
188 probe combined with an inflatable cuff to measure arterial blood pressure - for sedation, and
189 pulse oximetry, Doppler and electrocardiography for GA. Capnography was used only in the
190 intubated rabbits).

191 **Interventions**

192 A total of 27% of the procedures (n=57) were abdominal surgeries, of which 50 were female
193 neutering, three were caesarean-section, two were cystotomies and two were mass removals.
194 Thirty-five per cent of the procedures (n=73) were non-abdominal surgeries, including 63

male castrations, seven lumpectomies, two rhinotomies, and one ear surgery (TECA). The remaining 38% (n=80) were classified as minor procedures, accounting for 37 dental filings, 32 diagnostic images, six wound cleaning/dressing changes, three endoscopies, one tear duct flush and one blood sampling.

Perianaesthetic mortality

A total of 18.5% (n=10) of the rabbits died within 72 hours post-GA /sedation (95% confidence interval: 0.025 to 0.086; Table 2). Of these, 70% (n=7) had combinations of drugs which included both medetomidine and ketamine administered, and 80% (n=8) had been scheduled for elective procedures. None of the rabbits that died had undergone multiple anaesthetic events. In 70% (n=7) of the rabbits, the cause of death was attributed by the clinician in charge to cardiorespiratory complications. Univariate binary logistic regression did not identify any risk factor associated with perianaesthetic mortality (Table 3); for this reason, multivariate logistic regression was not performed. In the majority (70%; n=7) of the rabbits that died, underlying cardiopulmonary diseases were either revealed by diagnostics (one rabbit) or post-mortem examination (one rabbit), or suspected by the clinician on the basis of the clinical history (5 rabbits; Table 2).

Perianaesthetic gastrointestinal complications

All the rabbits involved in the study were administered either metoclopramide (0.5 mg kg^{-1} SC every 12 hours, Metoclopramide Hydrochloride; Hameln Pharmaceuticals; n=98 rabbits) or ranitidine (2-4 mg kg^{-1} SC every 12 hours, Zantac; GlaxoSmithKline; n=87 rabbits) to help prevent postanaesthetic gastrointestinal dysfunction. The occurrence of the latter was evaluated on the animals that survived the anaesthetic event for more than 24 hours; these, including the rabbits that underwent two anaesthetic events, accounted for 204 cases. A total

of 38% of these (n= 77 cases and 69 rabbits) developed gastrointestinal complications within 72 hours after the anaesthetic event (95% confidence interval: 0.314 to 0.446). The 14.5% of these rabbits (n=69) had undergone one sedation and one GA, and 8 out of these 10 experienced gastrointestinal complications after each anaesthetic event. Univariate binary logistic regression revealed age (p<0.001), body weight (p=0.003) and sex (p=0.001) as risk factors for postoperative gastrointestinal complications (Table 3). However, when these variables were compiled into a multivariate model, only body weight (p=0.01) was confirmed as a significant risk factor (Odds ratio: 1.96; 95% confidential interval: 1.170-3.270).

Discussion

The present study highlights that the incidence of perianaesthetic mortality in rabbits is still very high compared to dogs and cats, even higher than previously reported (Brodbelt *et al.* 2008). Moreover, an extraordinarily high incidence of non-fatal perianaesthetic gastrointestinal complications was reported, accounting for 38% of the anaesthetic events analysed in the study. Whilst no specific risk factors could be associated with death, larger body weight was found to increase the incidence of anaesthesia-related gastrointestinal complications.

A previous study suggested that endotracheal intubation may contribute to perianaesthetic mortality in cats (Brodbelt et al. 2007). Owing to some anatomical similarities, namely the relatively small body size and the predisposition to develop laryngeal spasm, we hypothesized that this could represent a risk factor also for pet rabbits. On the contrary, our findings did not prove this hypotheses, but seem to suggest that endotracheal intubation is safe if performed carefully and by experienced personnel. Indeed, intubation of the trachea

allows efficient oxygen supplementation and positive-pressure ventilation, which are essential for the prevention and treatment of hypercapnia and hypoxia (Brimacombe 1995).

The BSAH is a referral centre, which might have led to an unintended selection bias. Most of the rabbits enrolled in this study were admitted to the hospital for elective procedures and only a few of them were assigned an ASA grade of III or higher, with very few critical animals undergoing emergency surgery. Whilst this may explain why the ASA grade was found as a non-significant risk factor, it also poses the question why, in the study population, the incidence of both mortality and gastrointestinal complications was so high. Indeed, healthy animals are expected to experience fewer complications than those assigned to an ASA grade of III or higher (Biboulet et al. 2001; Hosgood & Scholl 2002; Brodbelt et al. 2008; Bille et al. 2012). As a possible explanation, the lack of significance of the ASA status as risk factor in the rabbits of this study could be due to the retrospective, and therefore potentially inaccurate, assignment of the ASA classification, based on information available in the medical record. Alternatively, the ASA classification might have failed to detect the animals at higher anaesthetic risk owing to the relatively old age of the study population. This could reflect the tendency of first opinion veterinarians to refer geriatric patients, that supposedly carry a higher anaesthetic risk, even when simple procedures are scheduled. However, we failed to identify age as a significant risk factor.

Regarding the timing of death, half of the mortality incidents occurred after recovery from anaesthesia, often after the rabbit had been discharged. The presence of underlying cardiopulmonary diseases was diagnosed or suspected in the majority of the animals that died. This is in agreement with the findings of a previous study, which found that 38% of the rabbits died from pre-existing cardiovascular and/or respiratory diseases, possibly exacerbated by anaesthesia, and that these mortality incidents accounted for 95% of the known causes of death (Brodbelt et al. 2008).

Alpha-2 agonists have been recognized as a risk factor for the development of peri-anaesthetic complications in rabbits (Grint & Murison 2008), and although our study failed to confirm these findings, it is worth considering that 70% of the rabbits that died had an alpha-2 agonist as part of the anaesthetic protocol. A type II error cannot be excluded, and it is possible that our methods failed to detect an effect of the alpha-2 agonist on perianaesthetic mortality. It is however worth considering that each rabbit receiving medetomidine that died had also received ketamine, which poses a new challenge in the interpretation of our findings. Beside alpha-2 agonists, the combination of medetomidine and ketamine, or possibly even ketamine alone, might have contributed to the negative outcome of these subjects.

With respect to the type of anaesthetic event, this variable was categorized as either "sedation" or "general anaesthesia", depending whether the anaesthetic protocol included either the IV administration of an injectable induction agent, or/and the delivery of an inhalational agent for induction and/or maintenance of anaesthesia. However, this also has important limitations, as high doses of alpha 2-agonists, especially when combined with other drugs, may also result in a deep level of sedation, possibly accompained by unconsciousness, even when administered IM.

Beside death, the occurrence of non-fatal gastrointestinal complications was another focus of this study. Unexpectedly, rabbits undergoing abdominal surgeries did not have a higher risk of developing postanaesthetic gastrointestinal complications. This seems to suggest that handling of the stomach and the intestine during surgery does not affect postoperative gastrointestinal function. However, it is worth considering that most of the abdominal surgeries were routine spaying, which are usually shorter than some complicated non-abdominal procedures. Interestingly, 14.5% of the rabbits that experienced gastrointestinal complications had undergone two anaesthetic events, and in 80% of them gastrointestinal impairment was detected both times. Although the two-month interval between sedation and

GA should guarantee a complete wash out of the anaesthetic agents and a full recovery of the gastrointestinal function, it is possible that the two anaesthetic events were not independent, and previous sedations could have predisposed to the development of gastrointestinal complications in these rabbits. As an alternative explanation, a subjective predisposition of the rabbits, possibly due to underlying, undetected gastrointestinal disease, cannot be excluded.

The duration of anaesthesia, as well as the use of alpha 2-agonists and opioids in a dose-dependent manner (Cooper et al. 2009; Maugeri et al. 1994), might, indeed, affect the gastrointestinal function more profoundly than the intraoperative manipulation of abdominal organs. Unfortunately, anaesthetic duration and drug dosages was not reported for all cases, which limits the possibility to investigate whether these variables could be risk factors. Decreased food intake and stool production might also result from inappropriately addressed perioperative pain. This would be difficult to rule out in the study population as, although the vast majority of the rabbits received analgesics as part of the anaesthetic protocol, details regarding pain assessment were missing.

The body condition score was not recorded for most of the rabbits, and this is an important limitation of this study that inarguably affects the validity of our findings, as this variable is regarded as a more reliable indicator of obesity than body weight. Although the rabbits enrolled in the current study were of different breeds, the small, comparable body size was a common denominator of the subjects whose data were used to analyse the variable “body weight”. Moreover, data from rabbits aged less than 6 months, which are more likely to weigh less than the adults, were excluded. Under these circumstances, it is reasonable to assume that body weight could be a good surrogate of body condition score, and that heavier rabbits were likely to be overweight.

Obesity increases the odds of developing cardiac, orthopaedic, metabolic and gastrointestinal diseases in humans (German 2006), and it may be assumed that the overweight rabbits included in this study had some underlying gastrointestinal dysfunction, possibly exacerbated by the anaesthetic event. However, obesity could have also predisposed the rabbits to perianaesthetic death by interfering with the respiratory mechanics and increasing the odds for cardiovascular diseases (Lotia & Bellamy 2008; Brodsky et al. 2002), which was not the case in the study population. Moreover, it is worth considering that in obese rabbits the risk of opioid-related gastrointestinal side effects might have been increased by calculating the drug dose based on total instead of lean body weight.

As a retrospective investigation, this study has many limitations. Although every effort was made to collect as much information as possible from the database, the use of historical records poses a challenge in terms of missing details, difficulties in identifying complications retrospectively, and the possible inability to identify all the anaesthetic events occurring within the study period.

Conclusions

Rabbits represent an anaesthetic challenge owing to their high risk of perianaesthetic mortality. Beside the risk of death, the incidence of non-fatal perianaesthetic gastrointestinal complications was also very high in study population despite the use of metoclopramide or ranitidine. It might be worth undertaking preventive measures such as using opioids consciously, encourage eating soon after recovery and use syringe feed in case of inappetence, especially when dealing with overweight rabbits.

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388

Table 1 Breeds represented in a study population including 185 rabbits sedated or anaesthetized at a referral centre for exotic pet animals.

Breed		**Number of rabbits**	**Percentage of rabbits**
Dutch	Dutch	8	4.3%
	Dutch-cross	1	0.5%
Dwarf	Dwarf	3	1.6%
	Dwarf-Lop	22	12%
	Netherland Dwarf	8	4.3%
	Norwegian Dwarf	1	0.5%
	Polish Dwarf	1	0.5%
Giant	Giant	1	0.5%
	British Giant	4	2.2%
Lionhead	Lionhead	12	6.5%
	Lionhead-cross	8	4.3%
Lop	English Lop	3	1.6%
	French Lop	8	4.3%
	Lop	9	4.9%
	Lop-cross	11	5.9%
Mini	Mini-lop	24	13%
	Mini-rex	3	1.6%
Rex	Rex	7	3.8%
	Rex-cross	1	0.5%
Others	Harlequin	1	0.5%
	Himalayan	1	0.5%
	Tan	1	0.5%
	Unknown breeds	47	25.4%

Table 2 Details of perianaesthetic mortality events occurring in 10 out of 185 rabbits sedated or anaesthetized, for a total of 210 anaesthetic events, at a referral centre for exotic pet animals.

Time of death	Alpha 2 agonists-based protocol	Anaesthetic protocol	Intended procedure	Cause of death and post-mortem details	ASA classification*
Induction	No	Midazolam + Buprenorphine	CT	Unknown, unsuccessful CPCR attempted†.	2
Induction	Yes	Medetomidine + Buprenorphine + Ketamine	Castration	Aspiration, confirmed by necropsy, unsuccessful CPCR attempted‡.	1
Induction	Yes	Medetomidine + Buprenorphine + Ketamine	Spay	Unknown. Mild myocarditis, hepatitis and nephritis of unknown origin revealed by necropsy, unsuccessful CPCR attempted†.	3
During surgery	Yes	Medetomidine + Buprenorphine + Ketamine	Castration	Cardiac arrest. Atipamezole was administered and unsuccessful CPCR attempted‡.	1
During surgery	No	Fentanyl + Propofol	Explorative laparotomy	Cardio-respiratory arrest preceded by bradycardia, unsuccessful CPCR attempted†.	3
Recovery	Yes	Medetomidine + Buprenorphine +	Spay	Sudden onset of pulmonary oedema possibly secondary to	2

		Ketamine		cardiac failure (non-confirmed)†.	
24 hours	Yes	Medetomidine + Buprenorphine + Ketamine	Spay	Unknown. Died suddenly at home despite uneventful and quick recovery from anaesthesia.	1
48 hours	No	Buprenorphine + Alfaxalone	Explorative laparotomy	Cardiac arrest preceded by clinical signs of upper airways compromise. Chest radiographs taken shortly before death showed signs of lung consolidation. Unsuccessful CPCR attempted†.	3
72 hours	Yes	Medetomidine + Buprenorphine + Ketamine	Dental	Unknown. Progressive worsening of general clinical conditions after discharge. Euthanised in consultation.	2
72 hours	Yes	Medetomidine + Ketamine	Dental	Unknown. Progressive worsening of general clinical conditions after discharge. Died during transport to the hospital.	2

*Retrospectively assigned by the authors based on data recorded on the patient file pertaining clinical history, results of the preanaesthetic physical exam and, when available, blood results of the rabbits.

†Orotracheal intubation performed during CPCR.

‡Orotracheal intubation performed at induction.

Table 3 Results of univariate binary logistic regression analysis of the hypothesized risk factors against perianaesthetic mortality and perianaesthetic gastrointestinal complications of 185 rabbits, for a total of 210 and 204 anaesthetic events, respectively, sedated or anaesthetized at a referral centre for exotic pet animals.

Variable	**Sub-category**	***p* value†**	**Odd ratio†**	**95% CI†**		***p* value‡**	**Odd ratio‡**	**95% CI‡**	
Anaesthetic depth (general anaesthesia or sedation)		0.311	2.325	0.454	11.896	0.444	0.694	0.272	1.771
Intervention	Minor procedure	0.727	-	-	-	0.002	-	-	-
	Non-abdominal surgery	0.945	0.947	0.204	4.406	0.563	1.227	0.613	2.455
	Abdominal surgery	0.465	0.507	0.082	3.141	0.008	0.346	0.159	0.755
Anaesthetic protocol (alpha 2-agonists-based or not)		0.851	0.857	0.172	4.261	0.443	1.290	0.673	2.475
Age (years)		0.803	0.964	0.722	1.287	0.000	1.263	1.120	1.424
Body weight (kg, n=112)		0.868	0.923	0.358	2.379	0.003	1.758	1.209	2.556
Sex (M or F)		0.945	1.048	0.273	4.020	0.001	2.653	1.482	4.748
ASA	ASA 1	0.170	-	-	-	0.006	-	-	-
	ASA 2	0.025	0.034	0.002	0.656	1.000	0.000	0.000	-
	ASA 3	0.046	0.050	0.003	0.953	1.000	0.000	0.000	-
	ASA 4	0.999	-	-	-	1.000	0.000	0.000	-
Endotracheal intubation (yes or no)		0.667	0.744	0.194	2.857	0.911	1.033	0.586	1.821

CI, Confidence Interval; †values for perianaesthetic mortality; ‡values for perianaesthetic gastrointestinal complications.