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Anaesthetic Variables and Complications in Guinea Pigs undergoing Anaesthesia

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1. Introduction

Guinea pigs (*Cavia porcellus*) are rodents belonging to the family Caviidae. They are widely used as pets and laboratory animals, as they are very docile and friendly animals with an increasing popularity.

According to the literature guinea pigs are one of the most difficult species to achieve safe anaesthesia (Flecknell 2015, Erhardt et al. 2012, Colby et al. 2020).

The Confidential Enquiry into Perioperative Small Animal Fatalities, also known as CEPSAF study, undertaken in the UK in the early 2000's recording anaesthetics and sedations in many veterinary centres, concluded that the anaesthetic- and sedative-related risks of death in guinea pigs is 3.8% and therefore considerably higher than in dogs, cats and rabbits (Brodbelt et al. 2008).

Underlying causes include that inhalational anaesthetic agents are responsible for severe secretion of saliva and bronchial mucus and especially sevoflurane was associated with severe respiratory depression in another study (Erhardt et al. 2012, Heide 2003). Furthermore, intubation is technically demanding and not always recommended and therefore adequate response to respiratory emergencies is not possible (Erhardt et al. 2012, Flecknell 2015, Eberspächer 2017). The incidence of post-anaesthetic complications, such as gastrointestinal disturbances, depression, anorexia and respiratory infections is described as relatively high (Flecknell 2015). Additionally, the reaction to injectable anaesthetic agents has been reported as highly variable in guinea pigs (Flecknell 2015, Colby et al. 2020, Green 1975). There is common sense in the literature that referral centres in general tend to have a higher mortality rate (Brodbelt et al. 2009). This is explained by more difficult referred cases and procedures and as well as students, that might eventually monitor the animals' anaesthetic and not having the experience to detect eventual complications during anaesthesia. The CEPSAF study also concluded that death happened most commonly in the postoperative period with >60% of cats and rabbits and nearly 50% of dogs dying in this period (Brodbelt et al. 2008).

To summarise, guinea pigs are a rodent species that is still very difficult to anaesthetise safely. For a better understanding of the underlying causes, this study was conducted to detect more anaesthetic variables that have an impact on the survival of this species. Furthermore, this retrospective study aims at surveying the current anaesthesia-related complications but also the mortality rate of guinea pigs presenting in the time period from 2014 to 2019 at the University of Veterinary Medicine in Vienna.

2. Literature Review

2.1. General Information about Guinea Pigs

Guinea pigs (Cavia porcellus), also known as Cavies, are small animals belonging to the family Caviidae and to the order Rodentia. Their native origin is in South America, where they have been and are still bred as a common food source in some countries (Colby et al. 2020). In Europe, they are often held as pets, as they have a very friendly character and are, unlike hamsters, rats and mice, diurnal animals, which suits them well as pets for children. Furthermore, they are frequently used as laboratory animals. In nature wild guinea pigs live in communal organisations with established male-dominated social hierarchies; once formed they are usually stable (Colby et al. 2020). The average lifespan of guinea pigs is between 5 to 7 years, onset of puberty is in females with four to six weeks and in males with five to ten weeks of age (Bishop 2002).

Cavies belong to the herbivores; therefore, they need a diet rich in raw fibre, ideally good quality hay with ad libitum feeding regime because they tend to eat up to 100 portions in 24 hours (Drescher et Hamel 2012). Furthermore, fresh food like fresh vegetables as well as herbs should be provided additionally (Grant 2014). Continuous feed intake is crucial for an efficient digestion, if guinea pigs fast for too long they will presumably develop a gastrointestinal stasis. Guinea pigs are coprophagic, which means that they regularly consume their appendix faeces directly from the anus or cage floor. This is important for several reasons: In this way they are able to acquire proteins of bacterial origin, vitamin K and vitamins belonging to the B-complex and they renew the intestinal flora by taking up their own intestinal bacteria (Drescher et Hamel 2012). If they are prevented from coprophagia, they will lose weight, digest less fibre and excrete more minerals in the faeces (Quesenberry et Carpenter 2012).

As with rabbits, the Calcium/Phosphor-ratio in the diet is important because Calcium is only eliminated by the kidneys, an excessive uptake might lead to a high concentration of calcium in the urine and the animals are prone to develop cristalline sediments, subsequently leading to urolithiasis (Drescher et Hamel 2012). Another similarity to rabbits is, that the bacterial flora in the gastrointestinal tract is

predominantly consisting of gram-positive bacteria. Therefore, treatments with antibiotics with a gram-positive spectrum efficacy should be avoided, as this can cause severe dysbiosis (Drescher et Hamel 2012). In case of antibiotic resistance the use of amoxicillin might be an option via the subcutaneous route but is strictly limited (Müller 2017).

2.2. Guinea Pig Anaesthesia

Although guinea pigs are relatively easy to handle, the anaesthesia of this species is rather difficult compared to other rodents, because the response to injectable and inhalational anaesthetics is often variable (Green 1975). It is assumed that this results especially from the relatively low body weight, a high metabolism rate and a difficult determination of exact body weight (Erhardt et al. 2012, Heide 2003, Colby et al. 2020). As with other animal species an easy application of the anaesthetics via the routes IM, IP and SC as well as a broad margin of safety are desirable (Green 1975). Furthermore, good analgesia and rapid loss of conscience should be granted (Green 1975).

Main complications during general anaesthesia that have been described include hypothermia, respiratory and cardiovascular depression and metabolic derailment (Erhardt et al. 2012). This situation is often tightened by insufficient monitoring measures, further described in the chapter 2.2.7, “Monitoring”. Therefore, the used anaesthetic agents should avoid stimulating bronchial secretion, as this can promote subsequent respiratory problems (Green 1975).

Postanaesthetic complications include respiratory infections, gastrointestinal disturbances, depressed behaviour and anorexia (Flecknell 2015).

2.2.1. Preanaesthetic Considerations

Guinea pigs are friendly and docile animals, however, they are easily susceptible to stress. When handling this species, one should always avoid lifting them with only one hand, because this might lead to a rupture of the lungs, spleen or liver (Erhardt et al. 2012). The handler’s second hand should always also support the pelvis (Erhardt et al. 2012).

The exact determination of the body weight is described as difficult, as this can vary between 20 and 40% due to the filling of the caecum (Heide 2003, Colby et al. 2020). This leads to an inevitable error in dosing injectable anaesthetics, that affects every anaesthetic (Heide 2003, Erhardt et al. 2012).

The fasting of guinea pigs prior to anaesthesia is discussed controversially in the literature, because they can easily develop hypoglycaemic states as well as dehydration and gastrointestinal disturbances (Erhardt et al. 2012, Henke 1998, Flecknell 2015). Two authors recommend fasting of guinea pigs to decrease the likelihood of food withholding in the pharynx and the risk of regurgitation and subsequently for aspiration pneumonia (Cantwell 2001, Colby et al. 2020). Another possibility would be to remove food in the pharynx with moistened cotton sticks or by rinsing the mouth with water prior to anaesthesia (Eberspächer 2017, Lennox et Capello 2008). Another advantage of fasting guinea pigs that has been claimed is that dosing anaesthetics works more accurately (Flecknell 2015). Due to the difficult endotracheal intubation, that is not routinely performed and the often-lacking intravenous access in this species, the reaction to complications in anaesthesia is often insufficient (Eberspächer 2017).

Furthermore, the guinea pigs presented for dental treatment are often already inappetent, which can result in secondary gastrointestinal hypomotility (Gabriel 2016). As guinea pigs have an adverse body surface to body weight surface, they are prone to develop hypothermia during anaesthesia. To decrease this risk, isolating paddings, electronic heating mats, warm water gloves or bottles, or forced-air warming systems like the “Bair Hugger™” system should be used. According to the literature infrared heating lamps should not be used routinely, as the heat might accumulate and only a warming of the superficial skin is achieved (Erhardt et al. 2012). To further prevent hypothermia, it is useful to shear as little fur as possible and to use as little alcohol for disinfection as necessary (Erhardt et al. 2012). In case the treatment with antibiotics is indicated, agents with gram-positive spectrum efficacy should be avoided, otherwise secondary dysbiosis might develop with strong probability (Gabriel 2016). Perioperative management including protection of the cornea by application of an eye

ointment, fluid administration and eventual emptying of the urinary bladder should be performed as well.

2.2.2. Routes of Administration

In this chapter the common routes of administration in the guinea pig are discussed.

intravenous:

The placement of an intravenous catheter is possible in the cephalic or saphenous vein (Erhardt et al. 2012). In practice it is often difficult because the skin of guinea pigs is comparatively thick and the veins are not well accessible (Drescher et Hamel 2016, Heide 2003, Eberspächer 2017). For intravenous administration the auricular vein, the femoral vein, the jugular vein, penile vein or the caval vein can also be used, whereas the penile vein and caval vein can only be punctured under anaesthesia (Flecknell et al. 2007, Erhardt et al. 2012). EMLA cream, including the local anaesthetics lignocaine and prilocaine, is recommend for a pain free venous puncture (Flecknell et al. 1990). In case EMLA cream is used, it should be considered, that onset of action can take 45 minutes to one hour (Flecknell et al. 2007).

intraperitoneal:

The intraperitoneal application can be used as an alternative to IV applications, e.g. emergency application of antagonists. It is well suitable for larger injection volumes and should be done paramedian approximately 2cm cranial of the pubic bone after shaving and disinfection (Drescher et Hamel 2016). Error rates up to 30% are described in rodents when performed without exercise and therefore not recommended by one author (Erhardt et al. 2012). In guinea pigs a volume up to 20ml can applicated via the intraperitoneal route (Flecknell et al. 2007).

intramuscular:

The intramuscular application is seen as method of choice by many authors (Drescher et Hamel 2016, Erhardt et al. 2012). There are several injection sites possible: The injection in the hamstrings, although the animals frequently show defensive and flight

reactions. Alternatively, an injection in the dorsal musculature can be performed, but only with an injection volume of less than 0.5ml (Erhardt et al. 2012). Furthermore, the injection in the cranial thigh musculature is another option described (Erhardt et al. 2012).

subcutaneous:

The skin caudal to the ears is considered as smoother and not as sensitive to pain than other skin areas, therefore this is the injection site of choice according to one author (Drescher et Hamel 2016).

Especially in animals with a higher BCS (body condition score) the application of anaesthetics via this route is relatively unsafe (Erhardt et al. 2012). Moreover, to achieve a sufficient anaesthetic plane, it is necessary to increase the calculated IM dosage by 30% (Erhardt et al. 2012). The maximum volume that can be injected via the subcutaneous route is 10-20ml (Flecknell et al. 2007).

oral:

The oral administration of anaesthetics is not suitable due to the slow and unreliable absorption. However, this route is widely used for the administration of analgesics (Erhardt et al. 2012). Therefore, it is best to place the syringe or buttoned cannula through the diastema. It is important to induce the swallowing reflex, so the animal does not aspirate (Drescher et Hamel 2016).

2.2.3. Intubation

Endotracheal intubation is an important part in general anaesthesia with many advantages like securing the airways, administration of oxygen and inhalational anaesthetics and it is the foundation for intermittent positive pressure ventilation (IPPV). Furthermore, monitoring via capnography is always more reliable if an endotracheal-tube (ET-tube) is used instead of a face mask.

In practice the endotracheal intubation of guinea pigs is seldom performed as they have a ring of tissue formed by the soft palate, the palatoglossal arches and the base of the tongue, which makes the intubation very difficult (Johnson 2010).

Intubation with the help of endoscopic systems is described by several authors (Lennox et Capello 2008, Miranda et al. 2017). There are two techniques for the indirect visualisation of the glottis: the side-by-side-technique, where the endoscope is used side by side with the endotracheal tube and the over-the-endoscope-technique, where the endoscope is placed within the endotracheal tube and is withdrawn once the tube has been entered in the tracheal lumen (Lennox et Capello 2008).

It is also possible to intubate guinea pigs with a purpose-made laryngoscope blade, which requires special skill (Flecknell 2015). According to other authors, intubation is not recommended because of the risk of damaging the larynx and of spreading food particles in the airways and should only be performed in emergency situations (Eberspächer 2017, Eberhardt et al. 2012, Heide 2003). In case the intubation is not possible during emergency situations, ventilation can also be performed by swinging the animal around the transversal axis (Erhardt et al. 2012, Gabriel 2016).

In rabbits and cats there are also supraglottis devices available called V-gel, which can be positioned on top of the larynx (https://www.pattersonvet.com/Supplies/ProductFamilyDetails/PIF_512917, access: 23.06.2020). Unfortunately, supraglottic devices are not available for guinea pigs.

2.2.4. Common Complications

Expected complications that might occur when anaesthetising guinea pigs include hypothermia, hypotension, hypoventilation as well as hypoxia, similar to the anaesthesia of other species. Due to small body size and difficult airway management, especially hypothermia and hypoventilation are further regarded in this chapter.

Causes for the hypothermia are the impairment of the physiological thermoregulation processes through the anaesthetic agents and loss of heat to the surrounding environment, that is even compounded by the unfavourable body volume to body

surface ratio (Flecknell et al. 2007). Further reasons are the slower metabolic rate as well as a decreased muscle tone during anaesthesia (Weidauer et Alef 2017).
Hypothermia results in an even more slowed down metabolism and consecutively prolonged recovery phase and is therefore to avoid (Erhardt et al. 2012). Moreover, negative impacts on the cardiovascular and on the respiratory system are described, up to cardiac arrest, as well as an impairment of hemostasis and a higher risk for wound infections, making the frequent control of body temperature even more important (Weidauer et Alef 2017, Flecknell et al. 2007).
To circumvent hypothermia there are various options available: Prewarming by use of infrared lamps, passive warming to reduce heat loss through a better isolation of the patient and active warming aiming to increase the inner body temperature (Weidauer et Alef 2017).
Active warming is achieved with help of convective warming systems, one popular system for example is the "BairHugger™". Especially when anaesthetising small pets it is still important to consider, that the surgical field is not compromised (Weidauer et Alef 2017). Furthermore, there are warming blankets of newer generations, for example the "HotDog ®", where the heat is led to the patient by conduction as well as radiation. In comparison to conventional warming blankets the risk of burning is much reduced (Weidauer et Alef 2017).
Another option is the "SnuggleSafe ®", a heating pad that can be heated in a microwave. With the "SnuggleSafe ®" monitoring of temperature is crucial because it might lead to burnings in too hot pads as well as hypothermia if the heating pad has cooled down unnoticed (Weidauer et Alef 2017). Warmed IV infusions are also a possibility to reduce heat loss during procedures, but in a present study in cats it was not sufficient to avoid hypothermia as a solely measure (Steinbacher et al. 2010).
Hypoventilation is defined by a p_aCO_2 or the $etCO_2$ above physiological limits (30-45mm Hg) (Eberspächer 2017). To evaluate these parameters either a blood gas analysis is needed (for p_aCO_2) or capnography/capnometry (for $etCO_2$). Essentiell for good capnography results are either ET-intubation, a larynx mask or a tight sitting mask on the animal's snout (Eberspächer 2017). For further information regarding capnography see 2.2.7.2. Because intubation in guinea pigs is very seldomly

performed, exact monitoring of the $etCO_2$ is often not possible. Thus, it is even more important to pay attention to the animals' respiratory rate to detect eventual respiratory depression early. As awake guinea pigs have already very high respiratory frequencies, a respiratory rate of less than 25 bpm should be regarded as severe respiratory depression and should be immediately treated (Eberspächer 2017).

2.2.5. ASA-Classification

There is no physical status classification especially for guinea pigs, therefore the American Society of Anesthesiologists (ASA) Physical Status Scale is used same as for other species as listed in Table 1. According to one study examining the variability in ASA Physical Status Classification (ASA-PSC) assignment, major discrepancies can occur by allocating the ASA-PSC, which should be kept in mind when usind the ASA-PSC for clinical, scientific and statistical purposes (Mcmillan et Brearley 2013).
In general, rodents possess a higher anaesthetic risk, resulting from their low body weight and their high metabolic rate (Erhardt et al. 2012).

Tab. 1: The current ASA Physical Status Classification system as published by the Academy of Veterinary Technicians in Anesthesia & Analgesia. https://www.avtaa-vts.org/asa-ratings.pml (Access: 27.05.2020)

ASA I	Normal healthy animal, no underlying disease Minimal Risk
ASA II	Slight risk, minor disease present Animal with slight to mild systemic disturbance, animal able to compensate Neonate or geriatric animals, obese
ASA III	Moderate risk, obvious disease present Animal with moderate systemic disease or disturbances, mild clinical signs Anemia, moderate dehydration, fever, low-grade heart murmur or cardiac disease

ASA IV	High risk, significantly compromised by disease Animals with preexisting systemic disease or disturbances of a severe nature Severe dehydration, shock, uremia, or toxemia, high fever, uncompensated heart disease, uncompensated diabetes, pulmonary disease, emaciation
ASA V	Extreme risk, moribund Surgery often performed in desperation on animal with life threatening systemic disease Advanced cases of heart, kidney, liver or endocrine disease, profound shock, severe trauma, pulmonary embolus, terminal malignancy
E	Denotes emergency

2.2.6. Choice of Anaesthetics

Premedication:

Premedication before induction has many advantages. First, it is possible to provide analgesia before the painful stimulus occurred. This technique is called preemptive analgesia (Erhardt et al. 2012). Second, the dosage of the anaesthetics can be reduced as well as the dosage of the induction agents because the agents potentiate each other (Erhardt et al. 2012). Furthermore, the patient is calmed down prior to anaesthesia leading to a smoother induction and anaesthesia (Erhardt et al. 2012).

Sedatives that can be used in the premedication include medetomidine or midazolam, depending on the health state, each in combination with butorphanol (Eberspächer 2017). To induce a good sedation for short and non-invasive procedures alfaxalone is also recommended (D'Ovidio et al. 2018).

Still, there are many other protocols to use as well, including ketamine, acepromazine, diazepam, fentanyl and dexmedetomidine (Flecknell 2015).

The literature suggests to add atropine to the premedication, especially when anaesthesia shall be maintained with inhalation anaesthetics because atropine can decrease the production of saliva and bronchial mucus through its parasympatholytic effect (Heide 2003, Eberspächer 2017). Nevertheless, respiratory problems can still occur, probably because of the reduction of ciliary clearance leading to inspissation of the saliva (Heide 2003).

Inhalation anaesthesia:

Advantages of induction with inhalational anaesthetics include only small impact on the animal's metabolism due to a low rate of metabolisation of the inhalational agents, the possibility of an exact regulation of the anaesthesia's depth and duration and a relatively less stressful induction (Heide 2003). Disadvantages described include the requirement of an anaesthesia machine, the irritant effect of inhalational anaesthetics on guinea pigs, leading to profound salivation (Heide 2003). Additionally, inhalational anaesthetics have a depressive effect on medullary respiratory neurons (Heide 2003). As already described, premedication with atropine is indicated when using inhalational anaesthetics only. According to one author the use of sevoflurane should be avoided at all because of hypersalivation and hypersecretion (Heide 2003). Another author describes successful use of sevoflurane in guinea pigs, despite the risk of hypotension and hypersalivation, also he did not complain respiratory side effects (Flecknell 2015). Furthermore, it is reported that the MAC value of isoflurane is lower compared to other rodents, concluding that guinea pigs tend to react more sensitive on that gas (Seifen 1989).

In case only inhalational anaesthetics are used, full body chambers are necessary for induction, after loss of conscience, masks surrounding the head or nose should be used (Erhardt et al. 2012). It should always be borne in mind, that inhalational anaesthesia with only isoflurane or sevoflurane does not provide analgesia.

Injection anaesthesia:

One advantage of injection anaesthesia is that guinea pigs almost never response with profound secretion of bronchial mucous, so the use of anticholinergics is not required

anymore (Erhardt et al. 2012). Furthermore, many anaesthetic agents can be antagonised. For sedation established protocols use midazolam and medetomidine, for surgical procedures the use of the combinations of fentanyl, midazolam and medetomidine or fentanyl, midazolam and xylazin are suggested (Erhardt et al. 2012). These protocols have the advantage, that they can be fully antagonised and are therefore better controllable.

The major disadvantage of injection anaesthesia is, that a surgical tolerance cannot be achieved by only one anaesthetic agent. Only a combination of agents provides hypnosis, muscle relaxation and analgesia (Erhardt et al. 2012). This requires certain knowledge about the anaesthetics and antagonists to use.

Also, the determination of the exact body weight of guinea pigs can be challenging, as already described in chapter 2.2.1. To be able to manage unforeseen dosage errors only reversible protocols should be used.

Balanced anaesthesia:

Balanced anaesthesia means the combination of injection anaesthetics and inhalation anaesthetics as well as anticholinergics and muscle relaxants (Erhardt et al. 2012, Martinez et Keegan 2007).

Thereby synergistic effects between the anaesthetic agents can be used to decrease the dose of each anaesthetic while unwanted side effects can be reduced (Erhardt et al. 2012). Usually induction is achieved with injection anaesthetics, further maintenance with inhalational anaesthetics (Erhardt et al. 2012). As balanced anaesthesia is well controllable, this provides another opportunity for anaesthetising guinea pigs.

2.2.7. Monitoring

Monitoring of the anaesthesia is important for two important reasons: first, vital parameters are being watched, allowing to react immediately to deviations of the physiological values. The physiologic vital parameters of awake guinea pigs are displayed in Tab. 2. Second, the anaesthetic depth and therefore surgical tolerance can be evaluated (Flecknell 2015, Erhardt et al. 2012).

It is distinguished between non-apparative, respectively clinical monitoring and apparative monitoring.

Tab. 2: Physiologic vital parameters of conscious guinea pigs according to the literature (Erhardt et al. 2012, Flecknell 2015).

	Erhardt et al. 2012	Flecknell 2015
Adult body weight	500-1500g	500-1000g
Body temperature	37.5-39.5°C	38°C
Respiration rate	100-130 bpm	120 bpm
Heart rate	150-280 bpm	155 bpm

2.2.7.1. Clinical Monitoring

Non-apparative monitoring includes all monitoring measures, that can be conducted with the own senses (Erhardt et al. 2012, Eberspächer 2017). Due to the small body size and depending on how the surgical drapes are placed, clinical observation can occasionally be difficult.

For monitoring of the anaesthetic depth, the following reflexes can be used: righting reflex, palpebral reflex, corneal reflex, ear pinch reflex, hindlimb withdrawal reflex and forelimb withdrawal reflex (Heide 2003). Loss of reflexes is reported in the documented order, regain of the reflexes is again vice versa (Heide 2003). In one study surgical tolerance was achieved after the loss of the forelimb withdrawal reflex, prior to that animals responded with vocalisations and rowing motions (Heide 2003). Nevertheless, the corneal reflex should not be used in routine, due to the sensitivity of the cornea (Heide 2003). Anaesthetic depth can also be assessed by changes in the pattern and depth of respiration, changes of muscle tone, changes in heart rate and blood pressure can be used (Flecknell 2015).

Respiratory function can be assessed by monitoring the respiratory rate, that can be counted on the basis of the thoracic excursions. Unfortunately, the respiratory rate does not allow conclusion to the respiratory efficiency as it does not give information about the tidal volume (Erhardt et al. 2012).

Similar to other species cardiovascular function is evaluated by several parameters: Capillary refill time, pulse palpation, colour of the mucous membranes, heart rate and temperature of the peripheral limbs (Eberspächer 2017).

2.2.7.2. Technical Monitoring

In this chapter the most common monitoring devices are briefly described in regard to their use in guinea pigs.

Pulse Oximetry:

Pulse oximetry measures oxygen saturation of peripheral arterial blood (Flecknell 2015). The probe of the pulse oximeters can easily be applied at the fore- or hindlimb (Erhardt et al. 2012). For a reliable measurement of the oxygen saturation the limbs should not be pigmented, otherwise common pulse oximeters can be utilised (Heide 2003). Possible error sources might be a local ischemia caused by a too tight fit of the probe, as well as by peripheral vasoconstriction, e.g. caused by α_2-agonists, and local hypothermia (Erhard et al. 2012).

Electrocardiography (ECG):

ECG monitors the electrical activity of the heart and heart rate. It does not give information about circulatory function (Flecknell 2015, Eberspächer 2017). For small pets adhesive electrodes or needle electrodes can be used (Eberspächer 2017). The maximum heart rate that can be displayed varies between 200 and 250bpm, limiting the use of some monitors in guinea pigs, as their physiological heart rate varies between 150 and 280bpm (Flecknell 2015).

Measurement of Blood pressure:

Blood pressure can either be measured invasively or non-invasively. Invasive blood pressure measurement gives reliable results, but it requires arterial cannulation, which is difficult in guinea pigs due to size problems and therefore not well suited as a routine procedure (Flecknell 2015, Eberspächer 2017). Non-invasive blood pressure can be

subdivided in the doppler method and the oscillometric method. According to one author non-invasive blood pressure measurement is often not reliable in small pets (Eberspächer 2017). A different study found that blood pressure measurement with the oscillometric method worked accurate in guinea pigs (Kuwahara et al. 1996).

Capnography:

Capnography allows measurement of the carbon dioxide partial pressure ($etCO_2$) in the respiratory air (Flecknell 2015, Erhardt et al. 2012). One requirement for capnography is either endotracheal intubation, a supraglottic device or a tight sitting mask on the animal's face (Eberspächer 2017). As this is often not possible in guinea pig anaesthesia, capnography can often not be used to its full extend. Another possibility is to use the capnograph in connection with a facial mask to be able to monitor respiratory rate. Nevertheless, end-tidal carbon dioxide ($etCO_2$) remains difficult to measure in small mammals because the side-stream technique samples too much gas volume of the animal's tidal volume and the mainstream capnography might introduce too much dead space into the breathing circuit (Flecknell et al. 2007).

Temperature Measurement:

The measurement of body temperature is one of the easiest monitoring measures (Flecknell 2015). Still, it is very important as the temperature of small animals like guinea pigs can rapidly decrease because of their unfavourable body surface to body volume ratio (Flecknell et al. 2007). In case of a drop of temperature below 35°C it must be borne in mind, that some thermometers stop measuring at this point, and onset of severe hypothermia might be overseen (Flecknell 2015).

2.3. Analgesia in Guinea Pigs

For an efficient pain management multimodal analgesia and preemptive analgesia are very useful. The multimodal approach means that analgesics of different classes are used. By this the single doses and with it the side effects can be reduced and by potentiation of the analgesics a more efficient pain treatment is achieved (Erhardt et al. 2012, Wenger 2012). Preemptive analgesia means the prevention of pain by

administration of analgesics prior to the pain stimulus (Erhardt et al. 2012, Wenger 2012).

Before proposing an analgesic plan, it is important to consider the health state of the patient, if contraindications against certain classes of analgesics exist, what kind of pain has to be treated, how long the pain might persist, whether it is acute or chronic pain and whether a multimodal approach is possible (Tacke et al. 2017).

2.3.1. Assessment of Pain

Recognition of pain and its intensity is crucial for effective use of analgesics. To the author's knowledge literature about pain assessment in guinea pigs is limited. As a prey species guinea pigs try to hide pain and freeze in their behaviour as soon as they detect an observer (Wenger 2012, Flecknell 2018). One author recommends observing guinea pigs for 15 to 30 minutes, but this might be difficult in clinical routine (Flecknell 2018). To assess pain in guinea pigs, it is useful to look at the external aspects of the animals to detect abnormalities in posture and fur (Flecknell 2018). Summoning the animals to move might reveal deviations in gait or untypical aggression and hiding behaviour (Flecknell 2018). It must be kept in mind that also healthy guinea pigs squeak and can freeze their behaviour (Flecknell 2018). Requirement for recognition of abnormal behaviour is always the knowledge of the species-specific behaviour.

Unidimensional pain scales can be implemented to objectify pain, e.g. the visual analog scale (VAS) or numeric scales (NRS) (Tacke et al. 2017). Multidimensional pain scales like grimace scales already exist for some laboratory animal species as rats, mice and rabbits (Sotocinal et al. 2011, Langford et al. 2010, Keating et al. 2012). Unfortunately, there is no grimace scale established for guinea pigs yet. One study concluded that observation at the cage-side is not a reliable assessment of pain, as guinea pigs are able to suppress pain behaviour as soon as an observer is present (Oliver et al. 2017). The authors rather suggest a combination of video recordings and test for mechanical hypersensitivity to detect pain more sensitive (Oliver et al. 2017). Nevertheless, video recordings might be too costly to implement them in clinical routine. In the same study an ethogram was published, listing passive behaviours with increasing frequencies as well as active behaviours with decreasing frequencing in

response to pain (Oliver et al. 2017). Passive behaviours included closed eyes, squinting, piloerection that affects more than 50% of the body surface, weight shifting, subtle body movements and incomplete movements (Oliver et al. 2017). As active behaviours body turns, head or neck movements, rearing, coprophagy and forward or backward movements were detected (Oliver et al. 2017). Another study suggested also changes from standing to lying down, especially with one leg straightened, writhing and flinching to be pain related behaviour (Ellen et al. 2016). Nevertheless, also this study group recorded the guinea pigs' behaviour by video and concluded, that the shown changes in behaviour were rather subtle (Ellen et al. 2016). Still, behavioural changes might also be induced to a certain extend by medication, for example by opioids and benzodiazepines, and should not be misinterpreted as signs for pain resulting in overdosing analgesics.

2.3.2. Current Analgetic Management in Small Mammals

A study conducted in the UK in 1996 found out that only 22% of vets used analgesics routinely in surgical procedures in small mammals, including rabbits, guinea pigs, ferrets and hamsters (Lascelles et al. 1999). The authors assumed lack of knowledge as the major cause (Lascelles et al. 1999). A similar study by the same authors was again performed in 2013. At this time, they found out that overall more analgesics have been prescribed perioperatively compared to the older study, but unfortunately this study concentrated on dogs and cats (Hunt et al. 2015). Nevertheless, this might have developed because of increasing awareness of animal welfare in veterinary practice (Hunt et al. 2015). This again was confirmed by a study conducted in New Zealand in 2011, with 77% of the practicing vets answering that their knowledge of pain assessment in rabbits and guinea pigs is insufficient (Keown et al. 2011).

2.3.3. Local Anaesthesia

Local anaesthesia is described as one of the easiest and most effective methods for preemptive analgesia (Gabriel 2016). Mode of action is by interrupting the transmission of pain in sensory, afferent neurons (Skarda et Tranquilli 2007). Similar to other species, local anaesthetics can be used in form of splash blocks, local infiltrations, topical, regional nerve blocks, epidural and intrathecal anaesthesia (Flecknell 2018).

One huge advantage is the reduction of other required general anaesthetics when they are combined with local anaesthetics (Skarda et Tranquilli 2007, Gabriel 2016). Furthermore, depending on the use of the local anaesthetic agent, analgesia might still be provided in the postoperative period (Skarda et Tranquilli 2007).
As dental treatments belong to the most common procedures in guinea pigs requiring anaesthesia and might be quite painful, local anaesthesia is peculiarly indicated (Gabriel 2016). Application of local anaesthetics at the periosteum and in facial portion of the skull is very painful and requires exact placement of the cannula (Gabriel 2016). Therefore, prior general anaesthesia is a requirement before application of local anaesthetics (Gabriel 2016).
Lidocaine and Bupivacaine are both suitable in guinea pigs (Flecknell 2018). For a faster onset of effect, both agents can also be mixed (Flecknell 2018). According to one author the application of local anaesthetics in small mammals for prevention of postoperative pain has been neglected until now (Flecknell 2018).

2.3.4. Systemic Analgesia

Unfortunately, there are only few studies about the dosage of analgesics in clinically relevant situations in guinea pigs. Most of the studies base on the reaction of otherwise healthy laboratory animals with controlled external circumstances. Therefore, dosages must be estimated carefully because the reaction of sick and moribund patients might differ (Flecknell 2018). Nevertheless, the most important analgesic classes and their agents regarding to guinea pigs are discussed in the next chapters.

2.3.4.1. Opioids

Opioids are analgesics with very strong pain-relieving properties and can act at the μ, ∂ and κ opioid receptors (Lamont et Mathews 2007). Opioid receptors are distributed in the central nervous system and periphery (Erhardt et al. 2012, Lamont et Mathews 2007). Due to the wide distribution of the opioid receptors, there are various side affects described. Functional ileus is one that is mentioned in the literature, but it is also stated that it only occurs occasionally and is preempted by the positive effects of analgesia, e.g. shorter time until the guinea pigs consume food again (Flecknell 2018). In case, a functional ileus is suspected the author recommends the additional

use of prokinetics (Flecknell 2018). Buprenorphine is the most frequently used opioid in small pets and it is especially popular because of its long duration of action of up to 8 hours, depending on dosage and species (Flecknell 2018). Despite of buprenorphine, the uses of butorphanol, meperidine, nalbuphine, pethidine and morphine in guinea pigs are described (Flecknell 2015).
Animals receiving opioids can either respond with central depression or central excitation, depending on the distribution and quantity of opioid receptors (Erhardt et al. 2012). These behavioural changes should not be misinterpreted as signs for pain.

2.3.4.2. Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) work by inhibition in the prostaglandin synthesis. Depending on the agent NSAIDs provide to a varying extend anti-inflammatory, antipyretic and analgesic effects (Lamont et Mathews 2007).
Due to a high incidence of older rabbits and guinea pigs, that have chronic kidney issues, it is recommended to applicate NSAIDs in the postoperative period predominantly (Flecknell 2018). Nevertheless, effective pain relief was achieved by the combination of meloxicam and a local anaesthetic block at the surgical site in one study (Ellen et al. 2016). Unfortunately, NSAIDs alone do not prevent acute intraoperative pain and do not potentiate the effect of anaesthetics unlike opioids (Tacke et al. 2017, Flecknell 2018). NSAIDs that can be used in guinea pigs include aspirin, carprofen, diclofenac, flunixin, ibuprofen, indomethacin and meloxicam (Flecknell 2015). Especially meloxicam is practicable, as it comes in an oral and injectable formulation (Flecknell 2018).

2.3.4.3. Tramadol

Tramadol is a weak opioid. Its analgesic effect relies on the inhibition of the serotonin and noradrenaline reuptake, leading to a stronger inhibiting activity of descending nociceptive tracts (Flecknell 2018).
Unfortunately, there were no studies found about the use of tramadol in guinea pigs. In rats and mice, effective analgesia has been reported (Raffa et al. 1992). However, current studies in rabbits suggest that oral bioavailability does not lead to effective plasma levels for pain relief as well as application of tramadol in rabbits was found to

influence the MAC value to only a small extend (Egger et al. 2009, Souza et al. 2008). Therefore, effectiveness of tramadol is not yet proven in guinea pigs and other analgesics should be chosen first.

2.3.4.4. Non-Steroidal Antipyretics

Metamizol is the main representative of the non-steroidal antipyretics. The effect is based on inhibition of central prostaglandin synthesis and opioid-like activity (Tacke et al. 2017). It is suitable in animals with contraindications against NSAIDs to provide good analgesia. Metamizol has spasmolytic effects and is therefore especially well suited for gastrointestinal illnesses and urolithiasis (Tacke et al. 2017). The tolerance of metamizol in small mammals is described as good and it can be applicated orally, intravenously and intramuscularly (Tacke et al. 2017).

2.3.4.5. Systemic Application of Local Anaesthetics

Local anaesthetics can also be administered systemically besides of nerve blocks, local infiltrations and epidural anaesthesia. In a current study in rabbits it could be shown, that animals that have underwent ovariohysterectomy and were treated with a lidocaine continuous rate infusion postoperative, had a better gastrointestinal motility, food intake and faecal output compared to the group treated with buprenorphine (Schnellbacher et al. 2017). Another advantage of lidocaine continuous rate infusion is the prokinetic effect on the gastrointestinal tract (Eberspächer 2017). Therefore, the authors recommend this alternative as postoperative analgesia method to minimize the risk for anorexia and gastrointestinal complications (Schnellbacher et al. 2017). At the time point of this study, there was no similar study found in regard to guinea pigs.

2.4. Postoperative Care

Most of the anaesthetic deaths happen in the postoperative period according to the CEPSAF study (Brodbelt et al. 2008). Therefore, surveillance and management are crucial in this critical time period. The following measures should be considered in every case: antagonisation of anaesthetic agents, temperature management, analgesics, fluid administration and food intake. Antagonisation of the anaesthetic agents should happen right after anaesthesia, in case the guinea pig is wakening very

slowly, one author recommends to antagonise a second time (Eberspächer 2017). It is described that the rear limbs can still hang loose up to 15 minutes after anaesthesia while the animal uses the forelimbs already for cleaning, as another author found (Heide 2003).

The time to consumption should be as short as possible because guinea pigs are prone to gastrointestinal stasis. Therefore, good quality hay and straw should be provided right after the procedure (Flecknell 2018). In case the animal is inappetent, assisted feeding should be considered (Eberspächer 2017, Erhardt et al. 2012). If the appetite is depressed, it might also be useful to administer a prokinetic drug like metoclopramide to stimulate gastrointestinal motility (Flecknell 2015). Food intake should not happen later than one to two hours after the procedure (Erhardt et al. 2012).

To assure an adequate degree of hydration, continuous fluid administration can be conducted either via the intravenous route or subcutaneously (Eberspächer 2017, Erhardt et al. 2012, Flecknell 2018). One should be careful with water bowls; the animals might get wet and develop hypothermia (Flecknell 2018).

Right after anaesthesia the unconscious animals should be placed in an environment with approximately 35°C (Flecknell 2018). When the animal is conscious is again, the environmental temperature can be reduced to 26-28°C according to one author (Flecknell 2018). Nevertheless, caution should be taken in patients with circulatory instability due to vasodilation (Weidauer et Alef 2017).

Sufficient analgesia should be provided before the animal regains consciousness again (Erhardt et al. 2012, Flecknell 2018). To reduce the stress level for the guinea pigs in the clinical environment it is possible to inform the owner about oral application of analgesics and consider discharge as early as possible (Flecknell 2018).

3. Hypothesis

To examine the influence of anaesthetic variables on the anaesthetic complications and survival rates of guinea pigs undergoing anaesthesia, the following hypotheses were postulated.

H0:

Anaesthetic variables included in the retrospective study do not influence the complications or survival rates of guinea pigs undergoing anaesthesia.

H1:

Anaesthetic variables included in the retrospective study influence the complications or survival rates of guinea pigs undergoing anaesthesia.

4. Material and Methods

4.1. Study Design

This study is a single-centre, retrospective elicitation of variables that might possibly influence the survival of anaesthetised guinea pigs.

During the time period between the 20th of July 2014 and the 20th of August 2019 the anaesthetic records and case files of the 245 guinea pigs that have underwent anaesthesia at the University of Veterinary Medicine were analysed.

4.2. Collection of Data

Source of the collected data were 245 case files, including the patient history of 139 guinea pigs, obtained from the clinic's digital hospital information system. The majority of written anaesthetic records was already digitalised and included in the case files, the remaining anaesthetic records have been looked up in the clinic's archive. The collected data has been imported to a spread sheet using Microsoft Excel 2016. Exclusion criteria were euthanasia due to poor prognosis, age under 3 months and patients missing the anaesthetic record. This led to an exclusion of 57 case files (Fig. 1). The exact time points of euthanasia are not all clear due to the retrospective nature of the study, this criterion was set to avoid counting deaths that led from the illness and not the anaesthesia.

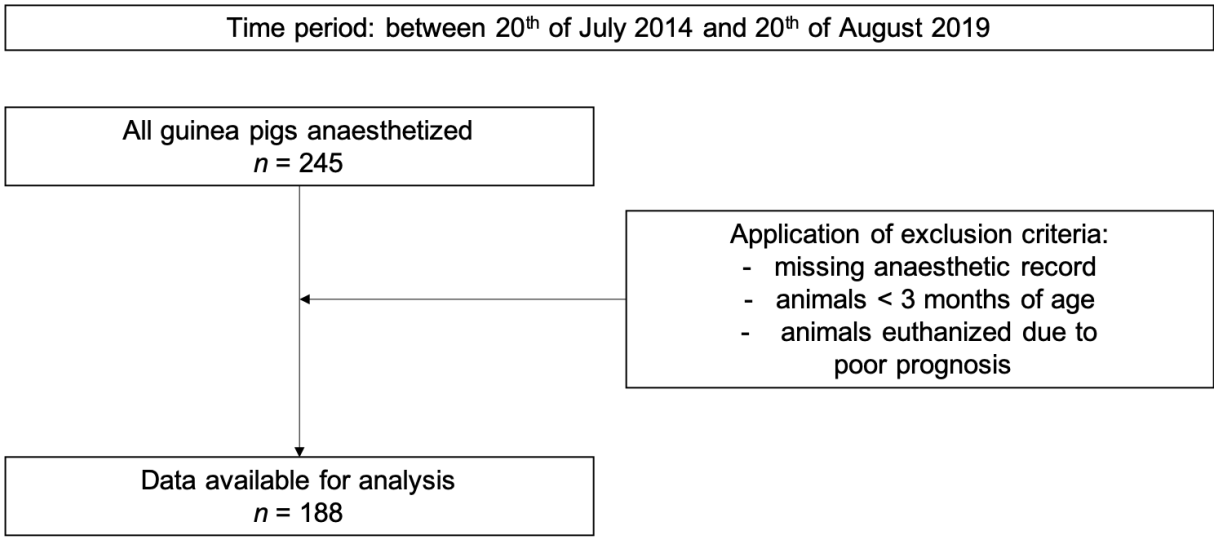

Fig. 1: Process of data collection for further analysis.

The aim was to exclude neonatal guinea pigs in the study, to avoid a risk factor coming from small age and does not apply to the entire population. According to the literature male and female guinea pigs have all reached puberty with 3 months of age (Bishop 2002, Müller 2017). Therefore, juvenile guinea pigs under the age of 3 months have been excluded. For a better overview the collected variables have been grouped into study population, anaesthetic regimen and procedure (Fig. 2).

Variables representing the study population were sex, age in months, presenting complaint(s), structured into organ systems, and pre-existing illness. To represent the

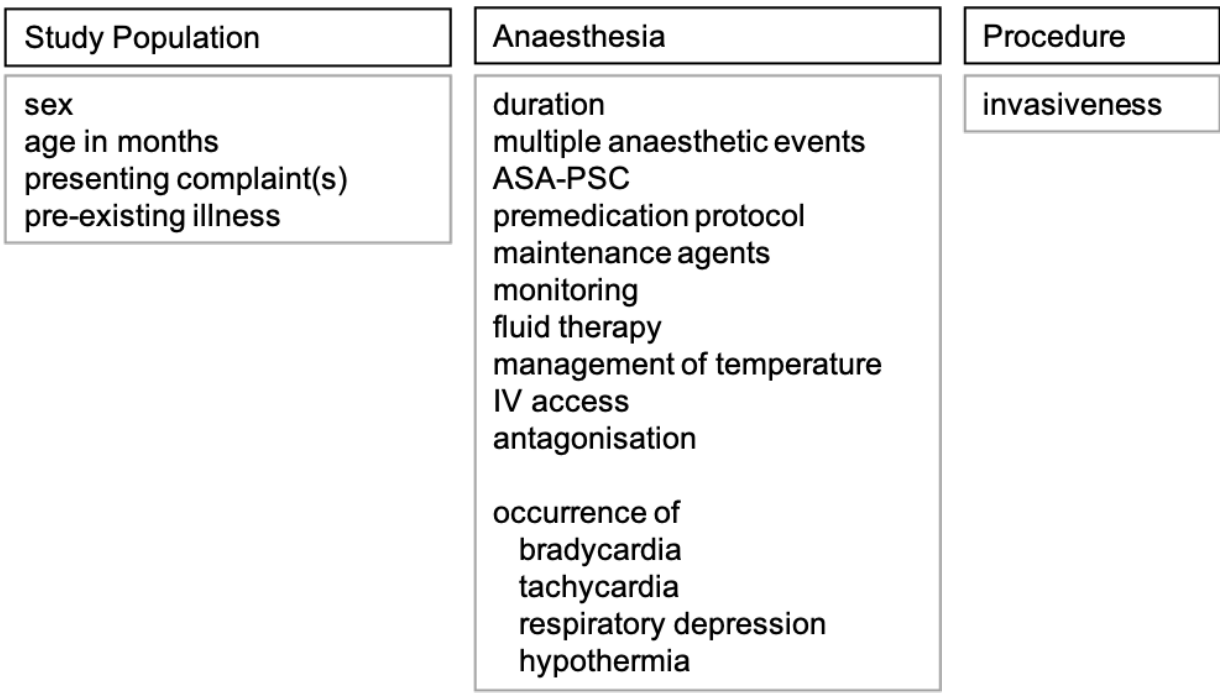

Fig. 2: Variables representing possible risk factors regarding the acute anaesthetic death. On the left side the variables concerning the study population are listed. In the middle the anaesthetic variables are documented. On the right side the procedure relevant variable is seen.

anaesthetic regimen the following variables were elevated: Duration of anaesthesia, multiple anaesthetic events, ASA Physical Status Classification, agents used for anaesthesia premedication and maintenance, type of monitoring, fluid therapy, management of body temperature, occurrence of bradycardia, tachycardia, respiratory depression and hypothermia, available intravenous access during the procedure and antagonisation of the anaesthetic agents. Procedure relevant data included the type of

procedure, whether it was a non-invasive (in all cases CT) or invasive procedure. Invasive procedures were further subdivided into procedures on the head, abdominal procedures, procedures on the limbs, thoracic procedures and other procedures.

Due to missing information about survival after 48h post anaesthesia in many animals, the hazard was defined as “acute anaesthetic death”, meaning that animals, that have died during anaesthesia, in the recovery period or post recovery, before they were discharged were counted (deaths up to 48h post anaesthesia; Fig. 3). Duration of the recovery period was retrospectively set to the first 3h post anaesthesia. Animals, that have been discharged on the same day as the procedure with no further information regarding their health state have been assumed to survive 48h after anaesthesia. A long-term follow-up after discharge was not conducted. With additional information in the case files it was concluded if the death might have resulted from anaesthesia.

The definition of anaesthetic death was adopted from the CEPSAF study which reads as follows: “perioperative death within 48h of termination of the procedure, except where death was due solely to inoperable surgical or pre-existing medical conditions, i.e. anaesthesia and sedation could not be reasonably excluded from contributing to the death” (Brodbelt 2009).

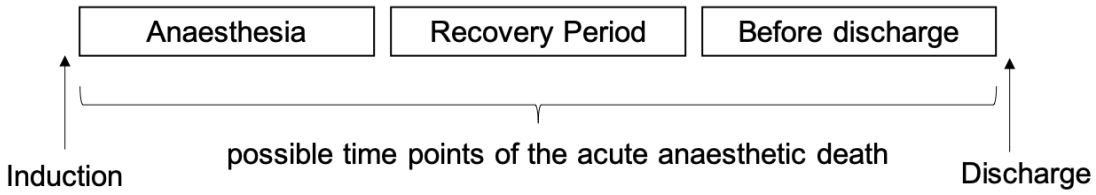

Fig. 3: Time points recording the acute anaesthetic death. Acute anaesthetic death was either recorded during anaesthesia, in the recovery period or before discharge.

4.3. Statistical analysis

The statistical analysis was performed using MedCalc (Version 19.3). If an animal underwent more than one anaesthesia, each event was regarded independently. As soon as the animal underwent its second or more anaesthesia, it was counted as a multiple anaesthesia. Univariate analysis, including frequency distribution was performed in all variables. The arithmetic mean and standard deviation were calculated

in variables with metric data: age in months, duration of anaesthesia, physiologic data of heart rate, respiratory rate and temperature at the end of the procedure. Based on the recorded physiological parameters it was extrapolated if the animals underwent bradycardia, tachycardia or hypothermia. The boundaries were set on base of the published physiologic data of guinea pigs by Erhardt et al. 2012, defining bradycardia with a heart rate smaller than 150 bpm, tachycardia with a heart rate higher than 280 bpm and a body temperature lower than 37.5°C. In the literature acute respiratory depression is described as a respiratory rate smaller than 25 bpm (Eberspächer 2017). The boundary for the duration of the procedure was set on base of the arithmetic mean. To have a round number for the further analysis the value of 50 minutes was chosen, instead of the exact arithmetic mean of 54.7 minutes. As the lifespan of guinea pigs is between 5 to 7 years, the boundary of 3 years or 36 months was chosen to be able to distinguish between rather young or old animals.

4.3.1. Odds Ratio

The odds ratio (OR) is the ratio of two odds (Porta 2008). In this study it describes the association between the event “acute anaesthetic death” and a variable. If the resulting OR value is smaller than 1, then the odds for the event are less likely to happen. In case the OR value is greater than 1, then the odds for the event are more likely. The OR was calculated using MedCalc (Version 19.3), also providing confidence intervals and significance level.

4.3.2. Two-day Mortality Rate after Anaesthesia

The formula for the two-day mortality rate was adapted from a formula for the death rate found in the literature (Porta 2008). The two-day mortality rate was calculated as follows:

$$two-day\ mortality\ rate = \frac{number\ of\ anaesthetic\ deaths\ in\ 48h}{number\ of\ guinea\ pigs\ anaesthetised} * 100$$

4.3.3. Cox Regression Analysis

The Cox Regression Model is a multiple regression model for analysis of censored survival data (Christensen 1987). To perform the Cox regression analysis a certain hazard must be defined, in this study this is the acute anaesthetic death. The hazard is assumed to be proportional for any two patients over time (Christensen 1987). The Cox regression model can be used to study and utilize the pattern of covariation of many variables with the hazard (Christensen 1987). Cox regression analysis and the corresponding Kaplan Meier plots were also performed using MedCalc (Version 19.3).

5. Results

5.1. Univariate Statistics

Of the 188 anaesthetic records, the following distributions as described in the following paragraphs and shown in tables 4, 5 and 6 could be seen.

Study population:

93 of the presenting animals were females, with 91 being intact females and 2 animals being neutered females. 94 male guinea pigs were counted, from which 43 animals were intact individuals and 51 being castrated animals. The sex of one individual was not assigned. The majority of the animals was older than 36 months old, 83 animals were 36 months old or younger ($\bar{x} \pm s$ = 41.9 ± 22.1, n=188). The most common main presenting complaints were because of dental reasons, 48.4% presented for this reason. 17.9% of the guinea pigs presented for reproduction matters. 12.6% were assigned to the organ system skin, having either superficial skin tumours, tumours of the mammary gland, bite injuries, lymphadenitis or abscesses without dental involvement. Only 2.6% presented with gastrointestinal problems, another 3.2% with Otitis, 3.2% with issues in the locomotory system, 5.8% with urologic diseases, 4.7% with ophthalmic problems and only 0.5% was assigned to respiratory problems and another 1.1% could not be assigned to the above-mentioned organ systems. These cases included osteopetrosis of unknown origin and osteodystrophy. Pre-existing illness was recorded in 36.4% of the guinea pigs. Only in 187 individuals were entries about pre-existing illness, leaving one guinea pig without entry.

Tab. 3: Distributions of the variables describing the study population. The *number (in italic)* next to the variable shows the number of datasets resulting from the anaesthetic protocols. There are 190 entries for the variable organ system of presenting complaint(s) because two guinea pigs were treated for more than one disease.

	Total	%
Overall	*188*	
Sex	*187*	
female total	93	50%
intact female	91	49%

castrated female	2	1%
male total	94	50%
intact male	43	23%
castrated total	51	27%
Age in months	*188*	
≤ 36	83	44%
> 36	105	56%
Organ System of presenting complaint(s)	*190*	
Gastrointestinal	5	2.6%
Dental	92	48.4%
Respiration	1	0.5%
Reproduction	34	17.9%
Reproduction - castration only	13	6.8%
Reproduction - pathologies only	21	11.1%
Urinary System	11	5.8%
Eyes	9	4.7%
Dermis	24	12.6%
Neurologic (Otitis media)	6	3.2%
Locomotory System	6	3.2%
Other	2	1.1%
Pre-existing-illness	*187*	
Yes	68	36.4%
No	119	63.6%

Anaesthetic regimen:

In 51.9% Anaesthesia duration was longer than 50 minutes, the arithmetic mean was 54.7 minutes. ($\bar{x} \pm s$ = 54.7 ± 34.8 min, n=160). The majority of animals, 67.6%, did not undergo anaesthesia more than once at the Vetmeduni Vienna. Only 5.9% of the guinea pigs were assigned to ASA 1, 57.2% of the study population were ASA 2, 34.2% were assigned to ASA 3, 2.1% were grouped to ASA 4 and only 0.5% were allocated ASA 5.

Analysis of the anaesthetic protocols showed, that the majority (86.2%) received an α_2-agonist in their premedication. 78.1% were given medetomidine and 8.6% were given dexmedetomidine. Midazolam was used in 47.6% of the premedication protocols, ketamine was given to 62.0% of the animals and alfaxalone was uses in only 3.1% of the cases. 74.3% of the animals received an opioid. The given opioids included butorphanol (51.3%), methadone (13.4%), buprenorphine (3.7%), fentanyl (4.3%) and morphine (1.6%). Maintenance of anaesthesia was achieved in 23.7% with isoflurane, in 35.1% with sevoflurane, in 32.5% with propofol, in 3.5% with ketamine and in 5.3% with alfaxalone. In 95.1% of the anaesthetic events at least one

instrument-based monitoring device was used. 89% of all cases were monitored with pulse oximetry, 25.3% were monitored with capnography, 52.2% with ECG, 29.7% did have temperature monitoring, and 7.1% had blood pressure monitoring. In all cases blood pressure was measured non-invasively. 57.3% of the animals received fluids during the procedure. Hypothermia prophylaxis was realised in 81.5%. Nevertheless, 62.7% of the animals were hypothermic (IBT < 37.5°C) after the procedure. Bradycardia was seen in 16.8%, tachycardia only in 2.5% of the anaesthetic protocols. Respiratory depression was documented in 35.2% of the cases. 56.4% of the animals had intravenous access via IV catheter. After anaesthesia the majority of animals (86.3%) was antagonised.

Tab. 4: Distributions of the variables describing the anaesthetic regimen. The *number (in italic)* next to the variable shows the number of datasets resulting from the anaesthetic protocols.

	Total	%
Duration in min	*160*	
≤ 50	77	48.1%
> 50	83	51.9%
Multiple Anaesthesia's	*105*	
Yes	34	32.4%
No	71	67.6%
ASA Physical Status Classification	*187*	
1	11	5.9%
2	107	57.2%
3	64	34.2%
4	4	2.1%
5	1	0.5%
Premedication	*187*	
alpha2-Agonists	162	86.6%
Medetomidine	146	78.1%
Dexmedetomidine	16	8.6%
Midazolam	89	47.6%
Opioids	139	74.3%
Butorphanol	96	51.3%
Methadone	25	13.4%
Fentanyl	8	4.3%
Buprenorphine	7	3.7%
Morphine	3	1.6%
Ketamine	116	62.0%
Alfaxalon	6	3.2%
Maintenance	*114*	
Isoflurane	27	23.7%
Sevoflurane	40	35.1%
Propofol	37	32.5%
Ketamine	4	3.5%

Alfaxalon	6	5.3%
Monitoring	*182*	
pulse oximetry	162	89.0%
Capnography	46	25.3%
ECG	95	52.2%
Temperature	54	29.7%
Blood pressure	13	7.1%
Yes	173	95.1%
No	9	4.9%
Fluid therapy	*178*	
Yes	102	57.3%
No	76	42.7%
Temperature Management	*184*	
Yes	150	81.5%
No	34	18.5%
Heart Rate	*161*	
Bradycardia	27	16.8%
Tachycardia	4	2.5%
Respiratory Rate	*125*	
Respiratory Depression	44	35.2%
Temperature post procedure	*75*	
Hypothermia	47	62.7%
intravenous access	*179*	
Yes	101	56.4%
No	78	43.6%
Antagonization	*183*	
Yes	158	86.3%
No	25	13.7%

Procedure:

30.3% of all procedures were non-invasive. These procedures were in all cases CT-scans. 32.4% of the animals had a procedure on the head, including all dental treatments. 17% had abdominal surgery and 4.3% had a procedure on the limbs. 30 cases or 16% of the procedures could not be assigned to one of the groups.

Tab. 5: Distributions of the variables describing the procedure. The *number (in italic)* next to the variable shows the number of datasets resulting from the anaesthetic protocols.

	Total	%
Type of procedure	*188*	
non-invasive procedure	57	30.3%
procedure on the head	61	32.4%
Abdominal procedure	32	17.0%
procedure on the limbs	8	4.3%
Thoracic procedure	0	0%
other	30	16.0%

5.2. Odds Ratio

In the following paragraphs only the significant results are discussed.

Study population:

Analysis of the study population showed, that animals presenting with gastrointestinal problems are eight times more likely to die from acute anaesthetic death, than animals not presenting with GI problems. Guinea pigs presenting with urinary tract disorders, e.g. urolithiasis, had a twenty times higher risk, compared to the animals with other complaints presenting

On the opposite, the animals presenting with dental problems had a significant lower risk to die from acute anaesthetic death.

Tab. 6: Calculated odds ratios for the variables regarding the study population. Animals presenting with gastrointestinal, dental and urinary tract problems had a significant higher or lower risk for short-time mortality after anaesthesia.

	OR	95% CI	p-value
Organ System of presenting complaint(s)			
Gastrointestinal	8.05	1.24-52.24	0.03
Dental	0.13	0.03-0.59	0.01
Urinary System	20.04	5.21-77.11	<0.0001

Anaesthetic regimen:

Calculation of the odds ratios regarding the anaesthetic regimen revealed, that healthy animals (assigned to ASA 1 and ASA 2) had a much lower risk to die, than animals that were considered as sick (assigned to ASA 3, 4 and 5). Furthermore, premedication including methadone possessed a higher risk, as well as the application of ketamine during anaesthesia maintenance. Also, it could be seen that ECG monitoring and monitoring with five devices increased the odds for the anaesthetic death. Occurring complications like bradycardia and respiratory depression increased the risk, too.

Tab. 7: Calculated odds ratios for the anaesthetic variables. It is showed, that sick animals, premedication with methadone, ketamine application during maintenance, ECG monitoring, monitoring with 5 devices, bradycardia and respiratory depression during anaesthesia lead to a higher risk to die from acute anaesthetic death.

	OR	95% CI	p-value
ASA Physical Status			
Healthy (1,2)	0.11	0.03-0.41	0.0009
Sick (3, 4, 5)	8.89	2.44-32.5	0.0009
Premedication			
Methadone	4.80	1.57-14.70	0.006
Maintenance			
Ketamine	8.17	1.05-63.41	0.045
Monitoring			
ECG	4.44	1.22-16.15	0.024
Categorical			
5 monitoring devices	7.76	1.20-50.39	0.032
Heart Rate			
Bradycardia	6.30	2.00-19.88	0.002
Respiratory Rate			
Respiratory Depression	10.16	2.09-49.46	0.004

Procedure:

Animals undergoing non-invasive procedures were proven to have a significant smaller risk to die from anaesthetic death. On the other hand, abdominal procedures increased the odds to die significantly.

Tab. 8: Calculated odds ratios for the invasiveness of the procedure. It can be seen that non-invasive procedure have a significant lower risk to lead to short-time mortality after anaesthesia. Abdominal procedures were found to have a significant higher odds ratio.

	OR	95% CI	p-value
Type of procedure			
non-invasive	0.06	0.004-1.033	0.05
abdominal	8.33	2.83-24.55	<0.001

5.3. Associations between the Variables

To detect eventual associations between the variables that showed high odds for short-time mortality after anaesthesia a X^2-Test was performed. Test results showed significant associations between the following variables, that were already proven to be associated with short-time mortality after anaesthesia.

Animals suffering from urinary disorders were found to be medicated with methadone, having abdominal procedures and also having respiratory depression during anaesthesia. Sick animals, meaning animals assigned to ASA-PSC 3, 4 and 5, were also found to be medicated with methadone, having ECG-Monitoring, tolerating bradycardia during anaesthesia and were found to undergo abdominal procedures. Other associations found were medication with methadone and abdominal procedures as well as bradycardia and respiratory depression.

Tab. 9: Associations found between variables with significant elevated odds ratios. UTD = urinary tract disease.

associated variables	p-value
UTD & Respiratory Depression	0.04
UTD & Methadone	0.02
UTD & abdominal procedures	0.0001
Sick & Methadone	0.0006
Sick & ECG-Monitoring	0.006
Sick & Bradycardia	0.03
Sick & abdominal procedures	0.0001
Methadone & abdominal procedures	0.0001
Bradycardia & Respiratory Depression	0.0005

5.4. Two-day Mortality Rate after Anaesthesia

The overall mortality rate of the presenting guinea pigs was 8.5% (1 in 12 animals, 16 in 188). 2.7% (n = 5) died during the procedure. 2.1% (n = 4) died in the recovery phase. The majority of guinea pigs, 3.7% (n = 7), died between recovery phase and discharge.

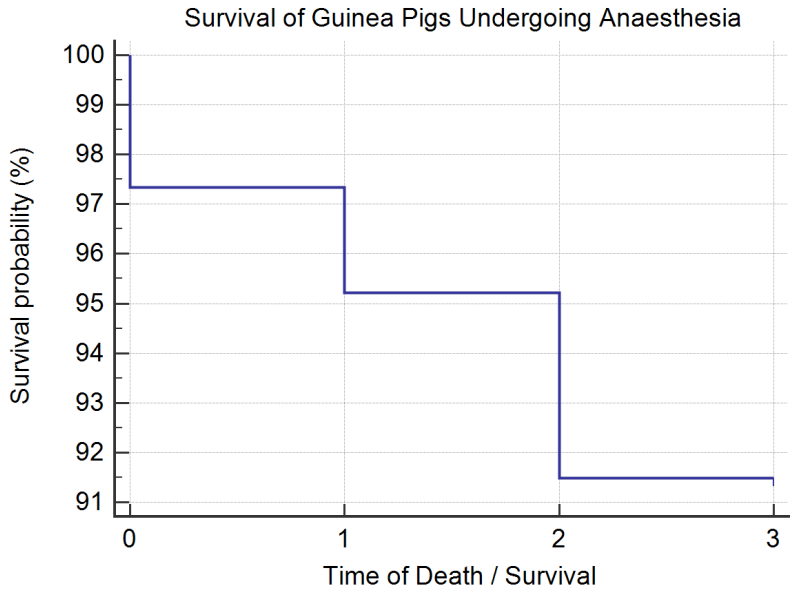

Fig. 4: Kaplan-Meier plot of the survival of all guinea pigs undergoing anaesthesia. The y-axis shows the survival probability in percentage. The x-axis shows the time points of death or survival: 0=death during anaesthesia, 1=death during recovery phase, 2=death after recovery phase and before discharge, 3=survival.

5.5. Results of Cox Regression Analysis and Kaplan Meier Plots

Study Population:

By analysing the hazard of the affected organ system on survival after anaesthesia, it could be observed, that animals presenting with urinary tract disease (52%) or gastrointestinal disease (56%) had a significant lower survival probability. However, the survival probability of guinea pigs presenting with dental problems was observed to be higher (97%) than of those presenting complaints in other organ systems (Fig. 5).

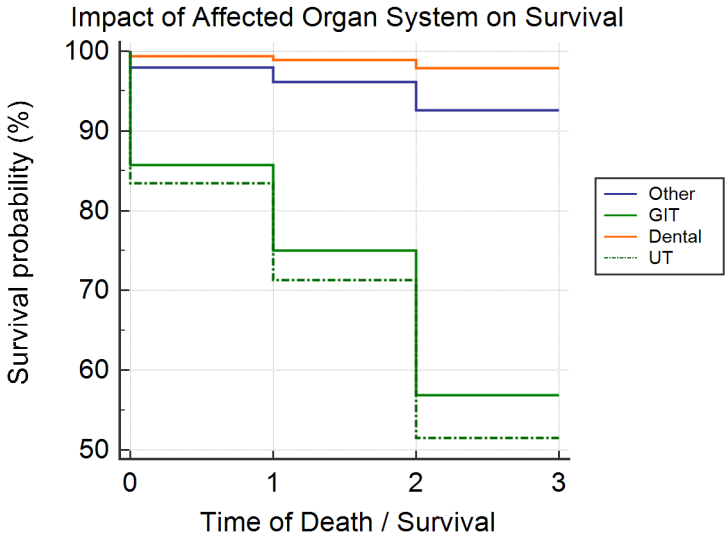

Fig. 5: Kaplan-Meier plot showing the survival rates of guinea pigs presenting with urinary tract disease, dental disease, gastrointestinal disease compared to those presenting with other complaints. The y-axis shows the survival probability in percentage. The x-axis shows the time points of death or survival: 0=death during anaesthesia, 1=death during recovery phase, 2=death after recovery phase and before discharge, 3=survival.

Anaesthetic regimen:

The corresponding kaplan-meier plots showing the survival probabilities of the variables testes significantly for the odds ratio are shown in Fig. 6. Cox regression of the variable ASA Physical Status Classification revealed the most significant result of the short-time mortality for sick animals of 18% ($p<0.001$). Animals assigned to the ASA-PSC three, four and five, were considered as sick animals. A lower survival rate could also be found for premedication protocols including methadone, here the calculation revealed a two-day mortality rate of 22% ($p<0.01$). Another risk factor found was ketamine applicated during maintenance of anaesthesia, cox regression analysis showed a short-time mortality after anaesthesia of 46% ($p<0.05$). Animals that have been monitored with an ECG during anaesthesia showed also a higher short-time mortality rate of 13% ($p<0.05$). Guinea pigs having a lower heart rate than 150 bpm during anaesthesia only had a survival rate of 75%, meaning a short-time mortality rate after anaesthesia of 25% respectively ($p<0.01$). In case of respiratory depression, meaning a respiratory rate of less than 25 bpm, occurred, the postoperative mortality found was 20% ($p<0.01$).

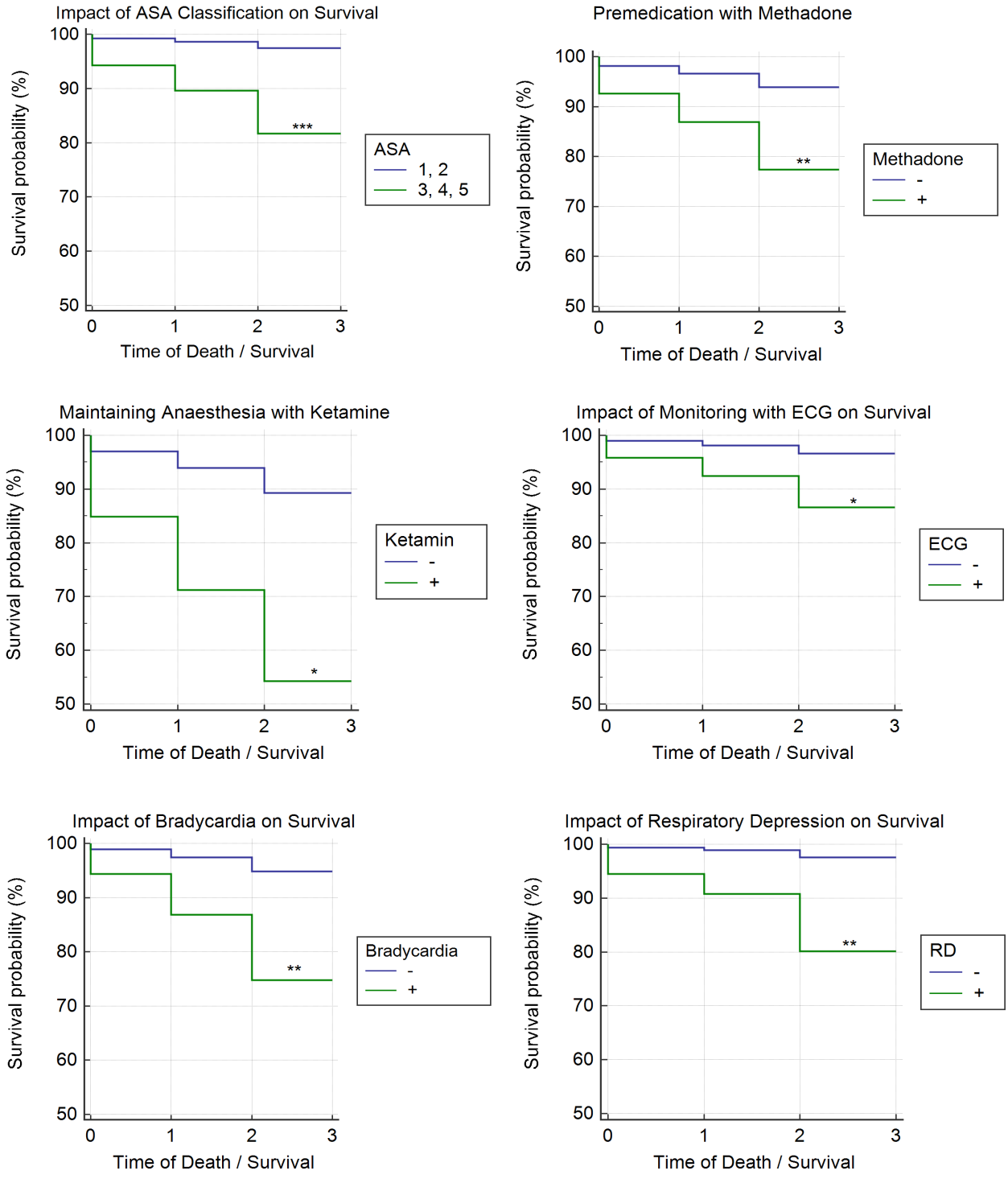

Fig. 6: Kaplan-Meier plots showing the survival rates of the animals regarded as healthy or sick (top left), animals premedicated with methadone or other premedication agents (top right), animals receiving ketamine during maintenance (middle left), animals monitored with ECG during anaesthesia (middle right), animals suffering from bradycardia during anaesthesia (bottom left) and animals suffering from respiratory depression (bottom right). Significance levels are indicated by * = $p<0.05$, ** = $p<0.01$, *** = $p<0.001$. The x-axis shows the time points of death or survival: 0=death during anaesthesia, 1=death during recovery phase, 2=death after recovery phase and before discharge, 3=survival. The y-axis shows the survival probability in percentage. For a better comparison survival probability (y-axis) has the same scale in all diagrams.

Procedure:

Cox regression analysis of the variable abdominal procedure revealed a two-day mortality rate after anaesthesia of 27% (Fig. 7). This is a significantly higher mortality rate compared to the animals not undergoing abdominal procedures ($p<0.001$).

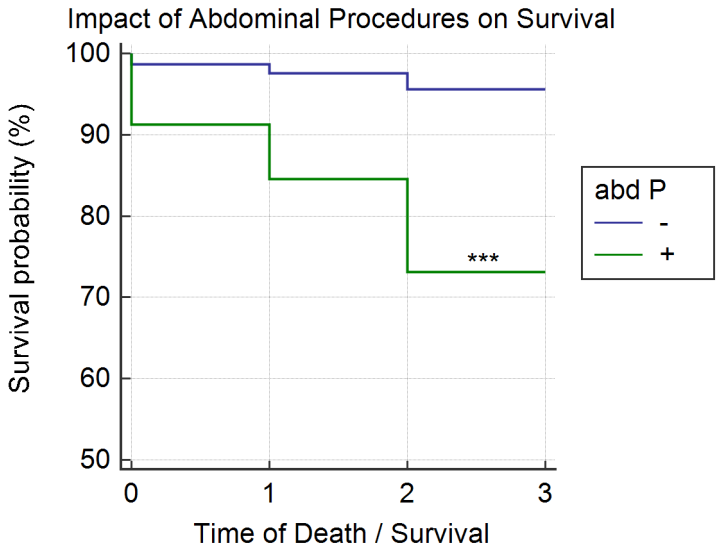

Fig. 7: Kaplan-Meier plot showing the survival rate of guinea pigs undergoing abdominal procedures. *** indicates a significance level of $p<0.001$. The y-axis shows the survival probability in percentage. The x-axis shows the time points of death or survival: 0=death during anaesthesia, 1=death during recovery phase, 2=death after recovery phase and before discharge, 3=survival.

6. Discussion

The findings from this study show that anaesthetic variables seem to influence the survival rates of guinea pigs undergoing anaesthesia at the University of Veterinary Medicine Vienna. Therefore, H0 can be confounded. The general mortality rate calculated was 8.5% (1 in 12) and therefore considerably higher than the risk of anaesthetic or sedative-related death of 3.8% in a recent study (Brodbelt et al. 2008). A higher mortality rate might be explained by the fact, that the University of Veterinary Medicine is a referral centre, therefore relatively more difficult cases with a compromised health state might have been presented. In the CEPSAF study not only referral institutions took part, but also smaller UK practices (Brodbelt et al. 2008). It is likely that at a teaching hospital also students with probably less anaesthetic knowledge are involved, but mistakes should happen there only seldomly as they are always under the supervision of an experienced veterinarian. Nevertheless, it must be borne in mind, that the methods in studies differ and caution must be taken when comparing mortality rates directly.

Surprisingly 62.7% of the guinea pigs had shown hypothermia at the end of procedure, although 81.5% had active temperature management during anaesthesia. This emphasises again how prone small animals are to hypothermia, in consequence of their unfavourable surface to volume ratio, as also described in the literature (Flecknell et al. 2007, Wenger 2012). In this study hypothermia could not be significantly associated with a higher mortality, but temperature management should still be part of the anaesthesia, as the disadvantages resulting from hypothermia, e.g. slower metabolism followed by prolonged recovery phase, should always be avoided (Erhardt et al. 2012). Wenger also stated that hypothermic guinea pigs are prone to anorexia, also a state always to avoid in guinea pigs (Wenger 2012). Furthermore, perioperative hypothermia is proven to depress the immune system (Beilin et al. 1998).

Another interesting finding in the univariate analysis was, that respiratory depression appeared in 35.2% of the animals. The boundary was set to a respiratory rate smaller than 25 bpm, which is in the literature already defined as severe respiratory depression and an emergency (Eberspächer 2017). Ventilation is only possible by swaying guinea pigs around their longitudinal axis, due to the lack of routine endotracheal intubation

(Eberhardt et al. 2012). Bradycardia as well seemed to be a very often occurring complication: 16.8% of the analysed anaesthetic protocols showed a heart rate lower than 150 bpm. In the further analysis bradycardia during anaesthesia was found out to be a risk factor.

Univariate analysis also showed that 56.4% of the guinea pigs had intravenous access. Unclear is, if the animals were not catheterised on purpose because they were only sedated lightly for diagnostic imaging for example, or if catheterisation did not succeed. In the literature there are several reasons described why IV access in guinea pigs is difficult (Drescher et Hamel 2016, Heide 2003, Eberspächer 2017).

Especially animals with digestive disorders and disorders of the urinary tract were proven to possess a significant higher risk compared to animals with complaints in other organ systems. Due to the very sensitive gastrointestinal system it seems logic that animals having already a compromised gastrointestinal balance, are more prone to die from anaesthetic death. Another theory was, that animals presenting with gastrointestinal processes might have had a vagal stimulation causing bradycardia and in consequence cardiac arrest, but this could not be proven as bradycardia and gastrointestinal disorders could not be linked.

On the contrary, animals presenting with dental problems appear to have a significant higher survival rate from anaesthesia. One explanation might be that many animals that have underwent a CT for further dental diagnostics were already grouped into dental organ system and the animals that have had dental treatment were exposed a much less-invasive procedure than those having abdominal surgery for example.

The time period with the highest risk in this study was the time between recovery phase and discharge, 3.7% of the animals died during that period. Due to small sample size, it was not further investigated what variables might have caused the different time points of death.

Surprisingly methadone was found to increase mortality significantly. The variables urinary tract disease, sick and abdominal procedures were associated with methadone. Association with respiratory depression was just not significant, but it is possible that this could have played a role, too, as one of the side effects of opioids described is respiratory depression (Erhardt et al. 2012, Flecknell 2016). Nevertheless,

it is also stated in the literature that opioid analgesia only rarely causes severe clinical problems in small mammals, including guinea pigs (Flecknell 2018). On base of this study's results it can only be concluded that combinations of abdominal surgeries (and therefore often urinary tract disorders) in sick animals premedicated with methadone possess a higher risk, but it cannot be said in what extend the variables contributed to the short-time mortality after anaesthesia. Therefore, the use of methadone in guinea pig anaesthesia should potentially be reconsidered, if the animal has a health state as described above. In any case, methadone does not commonly appear in the list of analgesics recommended for guinea pigs in specific text-books.

Maintaining anaesthesia with ketamine might also be a risk factor, but as only four guinea pigs had ketamine during maintenance, this result must be interpreted with caution. Still, ketamine is thought to compromise cardiovascular function when given IV at too high dosages. Due to the high weight of caecal and intestinal contents, the actual metabolically active body weight of guinea pigs can easily be overestimated with the result of accidentally overdosing (Colby et al. 2020). This is not only valid for ketamine, but all other injectable agents.

Sick animals were found to have a significant higher mortality rate than animals assigned to ASA 1 and 2. This result goes along with another author's findings in other animal species (Brodbelt et al. 2008). Another risk factor, that was found is monitoring the animals with ECG. This is linked to the finding, that sick animals were associated with ECG-monitoring. Of course, ECG is not a risk factor itself, because it is a non-invasive monitoring measure. One earlier hypothesis was, that maybe fewer monitoring measures applied during anaesthesia might increase the risk, but this could not be proved. The risk factors bradycardia and respiratory depression were also associated, this might be explained through the developing hypoxia resulting caused by severe respiratory depression (Erhardt et al. 2012). Severe respiratory depression was also related with urinary tract disease, but not to abdominal procedures. In case of renal failure animals often have a compromised acid-base balance, resulting in a metabolic acidosis, together with hyperkalaemia. In case a further vagal stimulation occurs, this can lead to bradycardia and later on to a cardiorespiratory collapse

(Erhardt et al. 2012, Wagener et Brentjens 2010). But as bradycardia could not be associated with urinary tract disorders, the exact reason remains unclear.

Due to the retrospective nature of this study, most of the entries in the anaesthetic protocols relied on standardised variables and were copied to the spread sheet. In some cases, e.g. ASA Physical Status Classification, the assignment to a particular class was not comprehensible, retrospectively. Another limitation was that a lot of anaesthetic records missed data. For the complications reported, it remains unclear how long the described complications have lasted. Although the original sample size was not small, the further analysis of the animals that have died from anaesthesia relied on a sample size of only 16 animals. This was also the reason, why the causes for the different time points of death have not been further analysed.

Another major limitation is, that there was no distinction between sedation and general anaesthesia possible, leading to an eventually different mortality rate as if only general anaesthesia would have been considered.

One recommendation for future research would be to undertake a prospective study, with an emphasised focus on the use of methadone, animals with urinary tract disorders, animals undergoing abdominal procedures and those with occurring complications like bradycardia and respiratory depression, to get further insight on the impacts they have on the survival of guinea pigs undergoing anaesthesia.

7. Zusammenfassung

Bis heute ist sich die Literatur einig, dass Meerscheinchen mitunter zu den Spezies gehören, in denen es sehr schwer ist eine sichere Anästhesie zu erreichen (Flecknell 2015, Erhardt et al. 2012, Colby et al. 2020). Unerwünschte Wirkungen bei der Verwendung von Inhalationsanästhetika, ein stark variierendes Körpergewicht abhängig vom Füllungszustand des Caecums, ein schwieriges Anästhesiemanagement aufgrund des raschen Wärmeverlustes, der kleinen Venen sowie das kontrovers diskutierte Management der Atemwege gehören mitunter zu den Gründen dafür (Heide 2003, Colby et al. 2020, Eberspächer 2017, Johnson 2010). Zusätzlich bleibt das Schmerzmanagement in dieser Spezies eine Herausforderung, da die meisten errechneten Dosierungen für den Gebrauch in gesunden Labortieren bestimmt sind und da die Schmerzerkennung fundiertes Wissen über das Verhalten von Meerschweinchen voraussetzt (Flecknell 2018, Oliver et al. 2017).

Diese retrospektive Studie wurde durchgeführt um Variablen erheben zu können, die das Überleben von anästhesierten Meerschweinchen beeinflussen. Dafür wurden 245 Anästhesieprotokolle der Meerschweinchen analysiert, die in einem Zeitraum über fünf Jahre an der Veterinärmedizinischen Universität Wien vorgestellt wurden. Die Ergebnisse zeigten eine Mortalitätsrate von 8.5%, die deutlich höher ist als in einer zuvor in der UK durchgeführten Studie (Brodbelt et al. 2008). Risikofaktoren, die ermittelt werden konnten, beinhalten Beschwerden im gastrointestinalen System sowie im Harntrakt bei der Vorstellung. Aufgetretene Komplikationen, die mit einem höheren Mortalitätsrisiko assoziiert waren, schließen Bradykardie und respiratorische Depression mit ein. Hypothermie trat in 62.7% der anästhesierten Tiere auf, konnte allerdings nicht mit einer erhöhten Mortalitätsrate assoziiert werden. Die Prämedikation mit Methadon scheint die Mortalität signifikant zu erhöhen. Methadon wurde vermehrt bei kranken Tieren (ASA 3-5) eingesetzt, speziell bei Tieren mit Erkrankungen im Harntrakt und Tieren, die im abdominalen Bereich operiert wurden.

Deshalb kann keine Schlussfolgerung gezogen werden in welchem Ausmaß diese Variablen zu der Mortalität nach der Anästhesie beigetragen haben. Folglich sollte der Gebrauch von Methadon in der Anästhesie von Meerschweinchen mit einem wie oben beschriebenen Gesundheitszustand hinterfragt werden.

8. Summary

Until today there is common sense in the literature that guinea pigs are one of the most difficult species to achieve safe anaesthesia (Flecknell 2015, Erhardt et al. 2012, Colby et al. 2020). Underlying causes include adverse reactions to commonly used inhalational anaesthetics, strongly varying body weight depending on the filling state of the caecum, difficult anaesthetic management because of rapid heat loss, small veins and the controversial debated airway management (Heide 2003, Colby et al. 2020, Eberspächer 2017, Johnson 2010). Additionally, pain management remains challenging in this species as many of the calculated dosages aim for the use in healthy laboratory animals as well as pain assessment requires profound knowledge about this species' behaviour (Flecknell 2018, Oliver et al. 2017).

This retrospective study was performed to elicitate variables that might influence the survival of anaesthetised guinea pigs. Therefore, anaesthetic records of 245 guinea pigs that presented at the University of Veterinary Medicine in Vienna during a five-year time period were analysed. Results show a mortality rate of 8.5%, that is considerably higher than in a previously conducted study in the UK (Brodbelt et al. 2008). Risk factors that could be found include presenting complaints in the gastrointestinal system as well as in the urinary system. Occuring complications associated with a higher risk to die from short-time mortality after anaesthesia comprise bradycardia and respiratory depression. Hypothermia occured in 62.7% of the anaesthetised animals but could not be associated with a higher risk to die. Anaesthetic premedication with methadone was found to increase mortality significantly. The use of methadone was directly associated with sick animals (ASA 3-5), especially those suffering from urinary tract disease and undergoing abdominal procedures. Therefore, a final conclusion to what extend these variables contributed to the short-time mortality rate after anaesthesia could not be drawn. Nevertheless, the use of methadone in guinea pig anaesthesia should potentially be reconsidered, if the animal has a health state as described above.

9. List of Abbreviations

ASA = American Society of Anesthesiologists

ASA-PSC = American Society of Anesthesiologists Physical Status Classification

BCS = body condition score

bpm = breaths per minute / beats per minute

CEPSAF = Confidential Enquiry into Perioperative Small Animal Fatalities

ECG = Electrocardiogram

ET = endotracheal

IM = intramuscular

IP = intraperitoneal

IPPV = intermittent positive pressure ventilation

IV = intravenous

NSAIDs = Non-steroidal anti-inflammatory drugs

OR = odds ratio

SC = subcutaneous

UTD = urinary tract disease

10. References

Academy of Veterinary Technicians in Anesthesia & Analgesia. https://www.avtaa-vts.org/asa-ratings.pml (Access: 27.05.2020)

Beilin B, Shavit Y, Razumovsky J, Wolloch Y, Zeidel A, Bessler H. 1998. Effects of mild perioperative hypothermia on cellular immune responses. Anesthesiology 89:1133-1140.

Bishop CR. 2002. Reproductive Medicine of Rabbits and Rodents. Veterinary Clinics of North America: Exotic Animal Practice 5(3): 507–35.

Brodbelt DC, Blissitt KJ, Hammond RA, Neath PJ, Young LE, Pfeiffer DU, Wood JLN. 2008. The risk of death: The confidential enquiry into perioperative small animal fatalities. Veterinary Anaesthesia and Analgesia.

Brodbelt D. 2009. Perioperative mortality in small animal anaesthesia. Veterinary Journal, 182(2): 152-61.

Cantwell SL. 2001. Ferret, Rabbit, and Rodent Anesthesia. The veterinary clinics of North America. Exotic animal practice, 4(1): 169–91.

Christensen E. 1987. Multivariate survival analysis using Cox's regression model. Hepatology, 7(6):1346–1358.

Colby LA, Nowland MH, Kennedy LH. 2020. Clinical Laboratory Animal Medicine – An Introduction. Fifth Edition. Hobokey, NJ: Wiley Blackwell, 212-242.

Descovich KA, Wathan J, Leach M, Buchanan-Smith H, Flecknell P, Farningham D, Vick S-J. 2017. Facial Expression: An under-utilized Tool for the Assessment of Welfare in Mammals. Altex, 34(3): 409-2.

Drescher B, Hamel I, Hrsg. 2012. Meerschweinchen: Heimtier und Patient. Dritte Aufl. Stuttgart: Enke Verlag.

D'Ovidio D, Marino F, Noviello E, Lanaro E, Monticelli P, Adami C. 2018. Sedative effects of intramuscular alfaxalone in pet guinea pigs (Cavia porcellus). Veterinary Anaesthesia and Analgesia, 45:183-189.

Egger CM, Souza MJ, Greenacre CB, Cox SK, Rohrbach BW. 2009. Effect of intravenous administration of tramadol hydrochloride on the minimum alveolar concentration of isoflurane in rabbits. American Journal of Veterinary Research, 70(8):945–949.

Ellen Y, Flecknell P, Leach M. 2016. Evaluation of Using Behavioural Changes to Assess Post-Operative Pain in the Guinea Pig (Cavia Porcellus). PLoS ONE, 11(9).

Erhardt W, Henke J, Haberstroh J, Baumgartner C, Tacke S, Hrsg. 2012. Anästhesie und Analgesie beim Klein- und Heimtier. Zweite Aufl. Stuttgart: Schattauer.

Gabriel S. 2016. Praxisbuch Zahnmedizin beim Heimtier. Erste Aufl. Stuttgart: Enke.

Green CJ. 1975. Neuroleptic Drug Combinations in the Anaesthetic Management of Small Laboratory Animals. Laboratory Animals, 9: 161-178.

Heide C. 2003. Zur Inhalationsnarkose unter Isofluran oder Sevofluran mit und ohne Atropin-Prämedikation beim Meerschweinchen. München: Ludwig-Maximilians-Universität.

Hunt JR, Knowles TG, Lascelles BDX, Murrell JC. 2015. Prescription of Perioperative Analgesics by UK Small Animal Veterinary Surgeons in 2013. Veterinary Record, 176(19): 493

Johnson DH. 2010. Endoscopic Intubation of Exotic Companion Mammals. Veterinary Clinics of North America - Exotic Animal Practice, 13(2): 273–89.

Flecknell PA, Richardson CA, Aleksandar Popovic in Grimm KA, Lamont LA, Tranquilli WJ, Editors. 2007. Lumb & Jones' Veterinary Anesthesia and Analgesia. Fourth edition. Ames: Blackwell Publishing, 765-783.

Flecknell P. 2018. Analgesics in Small Mammals. Veterinary Clinics of North America - Exotic Animal Practice, 21(1):83–103.

Flecknell P. 2015. Laboratory Animal Anaesthesia. Vierte Aufl. Oxford, Waltham: Elsevier.

Flecknell P, Liles JH, Williamson HA. 1990. The Use of lignocaine-Prilocaine Local Anaesthetic Cream for Pain-Free Venepuncture in Laboratory Animals. Laboratory Animals, 24: 142-146.

Grant K. 2014. Rodent Nutrition: Digestive Comparisons of 4 Common Rodent Species. Veterinary Clinics of North America: Exotic Animal Practice, 17(3): 471-483

Keating SCJ, Thomas AA, Flecknell PA, Leach MC. 2012. Evaluation of EMLA Cream for Preventing Pain during Tattooing of Rabbits: Changes in Physiological, Behavioural and Facial Expression Responses. PLoS ONE, 7(9):e44437.

Keown AJ, Farnworth MJ, Adams NJ. 2011. Attitudes towards Perception and Management of Pain in Rabbits and Guinea Pigs by a Sample of Veterinarians in New Zealand. New Zealand Veterinary Journal, 59(6): 305–10.

Kuwahara M, Yagi Y, Birumachi JI, Sekizawa SI, Tsubone H, Sugano S, Kobayashi H. 1996. Non-invasive measurement of systemic arterial pressure in guinea pigs by an automatic oscillometric device. Blood Pressure Monitoring, 1(5):433–437.

Langford DJ, Bailey AL, Chanda ML, Clarke SE, Drummond TE, Echols S, Glick S, Ingrao J, Klassen-Ross T, Lacroix-Fralish ML, et al. 2010. Coding of facial expressions of pain in the laboratory mouse. Nature Methods, 7(6):447–449.

Lascelles BDX, Capner CA, Waterman-Pearson AE. 1999. Current British Veterinary Attitudes to Perioperative Analgesia for Cats and Small Mammals. Veterinary Record, 145(21): 601–4.

Lennox AM, Capello V. 2008. Tracheal Intubation in Exotic Companion Mammals. Journal of Exotic Pet Medicine, 17(3): 221–27.

Martinez EA, Keegan RD in Grimm KA, Lamont LA, Tranquilli WJ, Editors. 2007. Lumb & Jones' Veterinary Anesthesia and Analgesia. Fourth edition. Ames: Blackwell Publishing, 419-437.

Mcmillan M, Brearley J. 2013. Assessment of the variation in American Society of Anaesthesiologists Physical Status Classification assignment in small animal anaesthesia. Veterinary Anaesthesia and Analgesia, 40(3):229–236.

Miranda A, Peêgo JM, Correia-Pinto J. 2017. Animal Facility Videoendoscopic Intubation Station: Tips and Tricks from Mice to Rabbits. Laboratory Animals, 51(2): 204–7.

Moritz A, Hrsg. 2014. Klinische Labordiagnostik in der Tiermedizin. Siebte Aufl. Stuttgart: Schattauer.

Müller K, Hrsg. 2017. HeimtierSkills, Praxisleitfaden zu Diagnose und Therapie bei kleinen Heimtieren. Erste Aufl. Stuttgart: Schattauer.

Oliver VL, Athavale S, Simon KE, Kendall LV, Nemzek JA, Lofgren JL. 2017. Evaluation of Pain Assessment Techniques and Analgesia Efficacy in a Female Guinea Pig (Cavia Porcellus) Model of Surgical Pain. Journal of the American Association for Laboratory Animal Science, 56(4): 425–35.

Porta M, Editor. 2008. Dictionary of Epidemiology. Fifth Edition. New York: Oxford University Press. 60-61.

Quesenberry KE, Carpenter JW, Hrsg. 2012. Ferrets, rabbits and rodents: clinical medicine and surgery. Third edition. Missouri, St. Louis: Saunders.

Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. 1992. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an “atypical“ opioid analgesic. Journal of Pharmacology and Experimental Therapeutics, 260(1).

Skarda RT, Tranquilli WJ in Grimm KA, Lamont LA, Tranquilli WJ, Editors. 2007. Lumb & Jones' Veterinary Anesthesia and Analgesia. Fourth edition. Ames: Blackwell Publishing, 395-418.

Schnellbacher RW, Divers SJ, Comolli JR, et al. 2017. Effects of Intravenous Administration of Lidocaine and Buprenorphine on Gastrointestinal Tract Motility and Signs of Pain in New Zealand White Rabbits after Ovariohysterectomy. American Journal of Veterinary Research, 78(12): 1359–71.

Seifen AB, Kennedy RH, Bray JP, Seifen E. 1989. Estimation of minimum alveolar concentration (MAC) for halothane, enflurane and isoflurane in spontaneously breathing guinea pigs. Lab Animal Sci, 39(6): 579-581.

Sotocinal SG, Sorge RE, Zaloum A, Tuttle AH, Martin LJ, Wieskopf JS, Mapplebeck JCS, Wei P, Zhan S, Zhang S, et al. 2011. The Rat Grimace Scale: a partially automated method for quantifying pain in the laboratory rat via facial expressions. Molecular pain, 7:55.

Souza MJ, Greenacre CB, Cox SK. 2008. Pharmacokinetics of orally administered tramadol in domestic rabbits (Oryctolagus cuniculus). American Journal of Veterinary Research, 69(8):979–982.

Tacke S, Gollwitzer A, Grammel L, Henke J. 2017. Schmerztherapie Bei Kleinen Heimtieren. Tierarztl Prax Ausg K 2017; 45(01): 53-60.

Wagener G, Brentjens TE. 2010. Anesthetic Concerns in Patients Presenting with Renal Failure. Anesthesiology Clin, 28:39–54.

Weidauer J, Alef M. 2017. Perioperatives Wärmemanagement. kleintier konkret, 20(03): 2–10.

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