

Use of ketamine and xylazine anesthesia in dogs: A retrospective cohort study of 3,413 cases

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ABSTRACT

The information regarding the risk of anesthesia-related death in veterinary medicine is scarce, and little is known about the mortality risk of specific anesthetics. The study conducted during 2019 at University of Sarajevo, Veterinary faculty, aimed to estimate the mortality risk of intermittent injectable ketamine-xylazine anesthesia in dogs and to investigate the potential relationship between mortality rate and anesthesiologists' experience. Anesthetic records, where ketamine and xylazine combination was used for anesthesia induction and maintenance, were reviewed and divided into two groups: inexperienced (AN1) and experienced anesthesiologists (AN2). Inexperienced anesthesiologists were constantly supervised by experienced ones, whose corrective interventions were recorded. Overall detected mortality rate was 0.15%, with 0.18% and 0.11% in the AN1 and AN2 groups, respectively. A statistically significant difference was not found. Records of the AN1 group revealed interventions of experienced anesthesiologist in 92% of cases. Detected mortality rate was within the values previously established for inhalant anesthesia indicating high safety in usage of investigated protocol, if performed by experienced anesthesiologists. The high percentage of interventions of a senior anesthesiologist suggests that supervised upskilling of inexperienced anesthesiologists before their independent work could result in a better outcome.

Keywords: Anesthesia, Dogs, Mortality rate, Ketamine, Xylazine

The reason for rising use of injectable anesthesia (IA) is the potential for adverse effects of volatile anesthetics on exposed surgical staff, recognized impact on global atmospheric pollution, and certain properties of injectable anesthetics that are absent in volatile ones (Posner and Buns 2009). In human medicine, among other indications, competency in IA is vital for the safe management of patients with malignant hyperthermia risk who require general anesthesia (Al-Rifai and Mulvey 2016). Certain injectable anesthetics, particularly ketamine, have become more intensively used because of their newly established benefits and novel indications. Increasingly, ketamine is used in emergency medicine because of the effect of reducing intracranial pressure while not reducing blood pressure or cerebral perfusion pressure (Morris 2009). Many studies report the use of ketamine and xylazine in general anesthesia in dogs at various doses and methods of administration and surgical indications (Hellebrekers *et al.* 1990, Mezerová *et al.* 1992, Naddaf *et al.* 2014, Abdel-Hady *et al.* 2017, Maksimović *et al.* 2019). However, investigating available literature non specifically describes the safety of their application and the mortality rate.

Furthermore, very often the available data on the degree of mortality in anesthesia is a summation of many different results and factors that are not specified by particular indicators (Brodbelt *et al.* 2008a, Bille *et al.* 2012, Gil and Redondo 2014). The quality of anesthesia services is highly correlated with perioperative mortality (Pignaton *et al.* 2016), and therefore poses an important factor to be defined for specific anesthetics and anesthesia protocols. Anesthesia safety depends on several factors and quality standards implementation, and the difference between developed and underdeveloped countries is well recognized (Bharati *et al.* 2014, Walker *et al.* 2014, Morrison *et al.* 2022). In this study, we investigated the mortality rate of bolus intravenous administration of ketamine and xylazine combination, the most common protocol of intravenous anesthesia in Bosnia and Herzegovina. The combination was used for the induction and maintenance of general anesthesia in dogs classified as 1 and 2 categories according to American Society of Anesthesiologists system (ASA). Anesthesiologists' experience as a potential indicator of mortality risk was also evaluated.

MATERIALS AND METHODS

Animals: An analysis of 3,413 documented anesthesia records of dogs undergoing general anesthesia for elective ovariohysterectomy and orchiectomy was performed. Clinically healthy dogs of different breeds and ages

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(33±17 months old) and body weight (17±8 kg) were included. Brachycephalic breeds were excluded. All dogs were classified into ASA 1 or 2 category based on pre-anesthetic physical examination and the body score condition assessment. Anesthesia records were divided into two groups. Preoperative, intraoperative, and postoperative procedures in the first group were performed by anesthesiologists with up to one year of experience in anesthesia (AN1), supervised by a senior anesthesiologist. The anesthesia records of this group also included information on whether intervention by the supervising anesthesiologist was required during any part of the procedure. The assistance of the supervising anesthesiologist followed in all cases when deviations from the protocol were significant enough that they could pose a danger to the quality of anesthesia or the patient's life. In another group, procedures were performed by senior anesthesiologists with a minimum of five years of experience in veterinary anesthesia (AN2). The number of dogs evaluated in the AN1 group was 1,628 and 1,785 in AN2 group. All animals were admitted 24 h preoperatively to adapt to the clinical setting. Food, but not water, was withheld for at least 8 h before anesthesia.

Ethical statement: Written informed consent was obtained from the owners of the dogs used for elective surgery in undertaken anesthesia protocols.

Analgesics and anesthetic regime: Induction and maintenance of general anesthesia was performed as previously described by Maksimović *et al.* (2019).

The analgesic protocol was based on the preoperative administration of NSAID carprofen (Rycarfa 50 mg/mL, Krka, Croatia) at a dose of 4 mg/kg subcutaneously and 2 mg/kg tramadol (TramadolSTADA 50 mg/mL, Hemofarm/Stada, Bosnia and Herzegovina and Germany) slowly intravenously. Tramadol administration was performed after the induction phase and confirmation of the dog spontaneous breathing. For rescue analgesia, morphine hydrochloride (morphini hydrochloridum 20 mg/mL, Alkaloid, Macedonia) was provided. Intraoperatively, before the skin closure, 1 mg/kg of lidocaine (Lidocaine hydrochloride 2%, Galenika, Serbia) was used for a subcuticular splash of the incision line. Lidocaine was also used for intratesticular anesthesia at a dose of 1 mg/kg in the preoperative preparation of males, after induction and ET intubation. During surgery, hydration of all animals with 0.9% sodium chloride at a maximum dose of 5 ml/kg/hour was maintained.

Depth of anesthesia was subjectively evaluated by assessment of the muscular tonus of the jaw, pupils' dilation, eyeballs position, palpebral and pedal reflex, response to surgery, and monitored physiological parameters (heart rate, respiratory rate, arterial haemoglobin oxygen saturation, and arterial blood pressure). Spontaneous movements were not allowed and the indicators for anesthesia maintenance were primarily heart rate or respiratory rate elevation and increasing of the palpebral reflex sensitivity. Extubation of the animal was done with positive gag reflex evaluation.

All dogs underwent observation for 48 h postoperatively. Postoperative analgesia was achieved using carprofen (Rycarfa® Flavor, Krka, Croatia) at a dose of 3 mg/kg once a day for the next three days. In the postoperative period, control of the surgical incision and assessment of the presence and quantification of pain (using University of Melbourne Pain Assessment Scale - UMPS) was performed. A point score of 10 or more points was considered as an indicator of the presence of moderate acute pain and the indicator for rescue analgesia. In the AN1 group, all assistance provided by a senior anesthesiologist during any part of the process were recorded.

Data analysis: Data distribution normality was estimated using a Shapiro-Wilk test. A chi-square test was used to determine the differences in mortality between the two observed categories concerning the experience of the responsible anesthesiologist. A $p < 0.05$ was considered significant.

RESULTS AND DISCUSSION

The overall detected mortality rate in the present study was 0.15%, with 0.18% in the AN1 and 0.11% in the AN2 group. There were no statistically significant differences in the detected mortality rates within observed groups of animals regarding anesthesiologists' experience. Nevertheless, anesthesia records of the AN1 group revealed that supervising anesthesiologists had to interfere once or more times per patient, in 1,498 (92%) cases. All documented deaths occurred in females, during (4 dogs) or after (1 dog) ovariohysterectomy, but with no observed surgical complications. The aim of the present study was to assess the anesthetic mortality rate of healthy dogs in a specific anesthesia protocol. Therefore, included only death cases which could not be explained by pre-existing medical or occurred intraoperative complications, similar to the investigations of Brodbelt *et al.* (2006, 2008a,b). In contrast, the investigation by Bille *et al.* (2012) included deaths from medical or surgical complications as well. The same study at the end of the investigation period defined the meeting point of the return of consciousness and the ability of the patient to maintain sternal recumbency. In this context, the authors concluded that setting the endpoint of 48 h after the procedure could have increased the death rate, as animals died in the postoperative period would then have been taken into account. In our study, the end point of the investigation was 48 h after the anesthesia, as recommended by Brodbelt *et al.* (2008a, b). Therefore, the established values should be a real indicator of the safe usage of the investigated anesthesia protocol and the established mortality rate.

The first prospective multicentre cohort study undertaken between 1984 and 1986 in the UK (Clarke and Hall 1990) reported anesthesia death risks of 0.12% in ASA 1 and 2 graded dogs. The same percentage of anesthesia death risks was observed many years later in the investigation of Bille *et al.* (2012). They concluded that generalization in defining mortality is not desirable, and it is necessary to clearly

define the specific factors in its definition. The mortality rate can be significantly affected only by anesthetic drugs used for the induction of general anesthesia, regardless of the anesthetic used for anesthesia maintenance. One of the protocols they investigated was the induction of anesthesia with ketamine (maintenance with isoflurane) which presented lower mortality in comparison to induction with thiopental (and maintenance with isoflurane), without a clear explanation for this finding. Previous studies found no correlation between the use of either ketamine or thiopental and anesthetic death (Dyson *et al.* 1998, Brodbelt *et al.* 2006, Brodbelt *et al.* 2008a). Brodbelt *et al.* (2008a) published cumulative incidences of anesthetic and sedation-related death of 0.17% in dogs, while estimated risks for healthy dogs (ASA 1–2) were 0.05%. The authors discussed significant differences in mortality rates observed between the animals in different ASA categories but did not debate the lower anesthesia death rate observed in healthy dogs in comparison to the result of Clark *et al.* (1990). In our study, the same combination was used to induce and maintain general anesthesia, and therefore safe usage of ketamine and xylazine for anesthetizing healthy dogs in elective surgery was demonstrated.

In general, the results of different studies of anesthesia death in veterinary medicine are notably higher than the 0.01 to 0.02% reported in human anesthesia (Biboulet *et al.* 2001, Newland *et al.* 2002). Brodbelt *et al.* (2008a), among other factors, as possible explanation mention the 'level of training of those involved'. In both human and veterinary anesthesiology, anesthesiologists' experience is a very important factor in anesthesia safety, both through the selection of anesthesia technique and patient monitoring and the adequacy of the response in resuscitation conditions (Dyson *et al.* 1998, Hosgood and Scholl 1998, Brodbelt *et al.* 2008a, Pignaton *et al.* 2016). The importance of veterinary technicians' education in anesthesia monitoring and the experience of the anesthesiologist greatly influences the outcome of the general anesthesia and surgical procedure (Dyson *et al.* 1998, Yosaitis *et al.* 2005, Hoffer *et al.* 2015). In our study, although no statistically significant, the difference between anesthesia death risks between two groups according to anesthesiologists' experience was observed (AN1 group 0.18% and AN2 group 0.11%). Furthermore, anesthesia records of the AN1 group revealed that supervising anesthesiologists had to assist, once or more times per patient, in 92% of cases. It is possible that the absence of the senior anesthesiologist could have resulted in an increase in the death rate in this group. The role of the anesthesiologist is continuous animal care, with postoperative recovery being imperative in the field of animal welfare for surgical patients. Therefore, the anesthesiologist must develop the skills in the fields of pharmacology, physiology, and clinical medicine (Verma *et al.* 2015). The level of competence of anesthesiologists in their work is crucial.

Regarding the time of death, anesthesia patients' deaths occur most of the time postoperatively in dogs

(47%) (Brodbelt *et al.* 2008a). In our study, four deaths were documented intraoperatively, while one death was recorded 2 h postoperatively. All established deaths were in females, which can be explained by the duration (Table 1) and invasiveness of the surgery, which is often dependent on each other. Ovariohysterectomy is a significantly more invasive and more demanding procedure than the orchietomy and requires a longer duration of general anesthesia (Gaynoret *et al.* 1999, Brodbelt 2009, Gil and Redondo 2014). In our study, all death cases did not have surgical complications.

Table 1. Mean duration time for anesthesia, surgery, anesthesia for animals with lethal outcome, and average duration time for anesthesia and surgery with average body weight for dogs with lethal outcome

Group	Mean duration time (min)			
	Anesthesia	Surgery	Anesthesia with lethal outcome	Surgery with lethal outcome
AN1	46±19	30 ±16	44±11	27±12
AN2	32±11	18 ± 9	48±3	33±8
<i>Average duration time (min) and body weight (kg) in total for dogs with lethal outcome</i>				
Anesthesia	Surgery		Body weight	
46 ± 9	30±11		11±3	

Defining the degree of mortality under general anesthesia is an extremely important tool in observing the progress of anesthesia techniques. However, the identification of risk factors is probably even more critical. The identification of such indicators of the risk of lethal cases in anesthesia ensures minimization or elimination of errors in the selection and procedure of anesthesia and enables their prevention, as well as the promptness and adequacy of anesthesiologists' reaction to their occurrence. The available results of studies of the mortality in small animals under general anesthesia are consistent in the identification and importance of specific factors such as breed, age, body weight, general health disorder, referral centre anesthesia, urgent procedures, extensive surgical procedures, specific medications and the use of volatile anesthetics alone in the induction of anesthesia (Bille *et al.* 2012). One of the factors that most studies concisely identify as the primary indicator of anesthesia safety is ASA classification. Some studies have shown the anesthesia risk is 3.26 times higher in ASA ≥ 3 categories (Bille *et al.* 2012) while some, in addition to this fact, emphasize age, intervention, and body weight in the evaluation of anesthesia factors (Brodbelt 2009). Nevertheless, Matthews *et al.* (2017) did not correlate body weight with the mortality rate under general anesthesia, which was not an important factor in our study either. Only ASA 1 and 2 dogs were included in our study, and a comparison between these categories in terms of mortality was not justified.

A lethal outcome can be caused even by solitary administration of sedative (Brodbelt *et al.* 2008a). The most commonly used sedatives in dog premedication are

$\alpha 2$ agonists, such as medetomidine, dexmedetomidine, and xylazine. Xylazine is thought to be less specific for $\alpha 2$ adrenergic receptors (Plumb 2011) and is, therefore, clinically less used to other drugs in this group. The use of xylazine in dogs, alone and with various general anesthetics, has been described in many studies. A search of the PubMed database, using the term 'ketamine and xylazine anesthesia in the dog', resulted in 53 wide-ranging studies (1975–2017). Many of the studies were based on several different protocols, such as the separate administration of ketamine and xylazine intramuscularly or intravenously, the use of ketamine and xylazine with the addition of phenothiazine, benzodiazepines, anticholinergics, muscle relaxants, or isopropyl phenol (Hellebrekers *et al.* 1990, Naddaf *et al.* 2014, Abdel-Hady *et al.* 2017). Also, combinations of ketamine and xylazine administration have been described, but at doses and modes of combination and administration different from the combination used in our study (Mezerová *et al.* 1992). According to the mode of administration, combination, and dosage of these two drugs, most similar to our study was investigation by Kim *et al.* (2015) who used a combination of sedatives and anesthetics at a dose of 1 mg/kg xylazine and 4 mg/kg ketamine intravenously. Unfortunately, the authors did not describe anesthesia maintenance, or whether they administered it at all. A search of the same term in the Web of Science electronic database revealed 190 research articles. However, by filtering the terms electronically and manually, it has been identified that only eight articles meet all the required criteria, where it describes the use of these drugs in a given animal model. From the above, it is clear that ketamine and xylazine, although extremely long present in veterinary medicine, have not been extensively investigated in terms of the effectiveness of their combined administration, route of administration, and dosages. To our knowledge, this is the first investigation that assessed the safety of general anesthesia induced and maintained by a combination of ketamine and xylazine in dogs.

General anesthesia is a drug-induced reversible condition of specific behavioural and physiological characteristics: loss of consciousness, amnesia, analgesia, and akinesia, while at the same time the stability of the autonomic system is preserved. Although it has been used for many years, as it does daily in a very large number of human and animal patients, the mechanism of achieving the beneficial effects of general anesthesia is still a very important question in medicine (Kennedy and Norman 2005, Brown *et al.* 2010, Hutt and Hudetz 2015). Anesthesia invariably carries a risk to the life of even healthy animals (Clarke and Hall 1990). Thus, it is not surprising that analysing morbidity and in particular, mortality is a clinically significant indicator of the efficacy and safety of anesthetics and by them produced general anesthesia (Cooper *et al.* 1984, Lee and Lum 1996). In general, any use of anesthetics, sedatives, and other medications entails a certain risk manifested by morbidity and/or ultimately mortality. It is important to emphasize that anesthesia-induced death has not been concisely defined in

veterinary medicine (Arbous *et al.* 2001). The main reason is a small number of intermittent studies which differ significantly in their methodology. Some do not specify ASA classification of patients, whether sedation or anesthesia death occurred, anesthetics and anesthesia protocols used, sedation, induction and/or maintenance of anesthesia, time of death (perioperative or postoperative death), or cause of death (Dyson *et al.* 1998, Gaynoret *et al.* 1999, Arbous *et al.* 2001, Brodbelt *et al.* 2008, Bille *et al.* 2012, Gil and Redondo 2014, Matthews *et al.* 2017). For this reason, it is difficult to compare different studies on anesthetic risk in veterinary medicine. In human pathology, cases of perianesthesia mortality of patients are divided into several categories that primarily relate to the patient's medical condition and anesthesia as a potential cause of death. Anesthesia, as the cause of the lethal outcome, is only considered if all other potential factors are excluded. A similar system is used in veterinary medicine, but pathological inference does not necessarily provide a definite cause of death (DeLay 2016).

Referring to the established overall mortality rate, described intravenous bolus combination of ketamine and xylazine for the anesthesia induction and maintenance pose an acceptable anesthetic protocol for dogs within ASA 1 and 2 categories. The results indicate that the observed mortality rate is within the values presented by other studies using volatile anesthetics, which is considered as the standard of good practice. It was observed that a high percentage of cases where the intervention of a senior anesthesiologist suggest that supervised upskilling of unexperienced anesthesiologists could provide higher patient safety and reduced anesthesia-related mortality.

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