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Research article

PHYSIOLOGICAL EFFECTS OF BALANCED ANESTHESIA DURING DENTAL PROCEDURES IN BROWN BEARS (*URSUS ARCTOS*)

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The goal of the present study was to monitor the physiological effects of a standardized balanced anesthetic protocol in brown bears (*Ursus arctos*) during routine dental procedures. Physiological parameters (rectal temperature, heart rate, respiratory rate and oxygen saturation) were evaluated in twelve brown bears, anesthetized with a balanced drug combination for 90 minutes during dental procedures. The animals were kept in the „Park for Dancing Bears" Belitza, Bulgaria. A standardized premedication protocol of a combined intramuscular injection of tiletamine HCl and zolazepam HCl (Zoletil 100® Virbac, France) 1mg/kg, medetomidine HCl 0.003mg/kg and 0.05 mg/kg of butorphanol was administered intramuscularly. Anesthesia was induced intravenously with a combined bolus of ketamine at 2 mg/kg and propofol at 2 mg/kg, and maintained with a constant rate infusion (CRI) of ketamine at 0.8 mg/kg/h and propofol 0.04 at mg/kg/min. Rectal temperature decreased significantly during anesthesia, whereas: heart rate, respiratory rate and oxygen saturation were stable with no significant changes in these parameters for the duration of anesthesia. In conclusion, this anesthetic drug combination is suitable for oral surgery of medium duration in brown bears.

Key words: Ursus arctos, balanced anesthesia, ketamine, propofol, medetomidine, zolazepam, butorphanol.

INTRODUCTION

Therapeutic manipulation and prophylactic treatment of wild brown bears routinely necessitates anesthesia. Safety of both the patient and personnel requires the patient remain on a stable anesthetic plane with minimal effects on the baseline physiological parameters. To achieve this, in-depth knowledge of anesthetic protocols and their effects in this specific species is necessary on the part of all involved staff. In general, the brown bear is a species relatively easy to anesthetize. Working with this species

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presents a relevant risk to the staff, and in-depth knowledge of the methods of anesthesia is mandatory.

Brown bears, like other monogastric mammals, have a pronounced tendency to vomit during induction and regurgitate while under anesthesia [1]. Consequently patients should be fasted prior to anesthesia. Historically different anesthetic combinations have been used in brown bears. The combination of zolazepam and tiletamine (Zoletil 100 ®) is widely used, despite the absence of an antagonist and often observed prolonged effect, with recovery times reaching up to several hours [2-4]. The combination zolazepam - tiletamine - medetomidine is also an effective anesthetic protocol for brown bears [5]. The advantages of the latter combination include relatively small drug volumes, which is important when delivering via darts, and partial reversal of anesthesia with atipamezole. This combination may however lead to hypertension and hypoxemia in black bears (*Ursus americanus*) and polar bears (*Ursus maritimus*) [6,7]. Medetomidine is often used in combination with other drugs such as ketamine and butorphanol for anesthesia of different non-domestic species [8-10]. As with zolazepam-tiletamine, adding medetomidine as an alpha-2-agonist helps to reduce the dose of other drugs, such as ketamine and butorphanol, administered in a single anesthetic protocol included in the scheme. Butorphanol, a morphinian-type opioid with partial agonist and antagonist activity, provides analgesia and moderate tranquilizing effects and can be included in balanced anesthetic protocols of bears applied in schemes of anesthesia of bears as a part of a balanced anesthetic approach [11]. Spontaneous recovery has been reported when using ketamine, an NMDA receptor antagonist, at induction to be considered as a possibility, when ketamine is included in anesthetic schemes [12,13]. A simple solution is to administer ketamine via constant rate infusion (CRI) versus single dose administration. The use of a medetomidine and ketamine combination can cause bradycardia [6]. A propofol infusion in bears ensures adequate control of anesthetic depth and safety during anesthesia. The doses and respective side-effects of the used drugs may be reduced using a balanced multimodal approach by including anesthetics with different pharmacological actions.

MATERIALS AND METHODS

The goal of this study is to determine how a balanced anesthetic protocol influences basic physiological parameters in brown bears.

Study scope and subjects

The study included twelve captive brown bears located at the “Four Paws” park for dancing bears near Belica, Bulgaria. The park is located in the Rila Mountains, near Belica, and covers an area of 12 ha at an altitude of 1350m. The survey was conducted in September 2014. Bears were free-range within the park area and were fed in specifically designated areas (zones) where food was provided in feeders. At the time of the study none of the bears were in hibernation. Age, sex and body mass of all subjects are represented in Table 1. The bears are raised free in the park area and twelve hours prior to anesthesia patients were sequestered in individual holding pens to facilitate pre-anesthetic manipulation and ensure fasting. The bears were anesthetized for a routine dental examination and procedures were performed as needed (tooth extraction, pulptotomy, etc.). Food was withheld 12 h before the start of anesthesia.

Table 1. Age, sex and weight of the bears

№	Age (years)	Sex	Weight (Kg)
1	18	F	110
2	16	F	100
3	22	F	150
4	27	M	250
5	24	F	100
6	14	F	120
7	21	F	130
8	28	M	200
9	24	F	130
10	16	M	220
11	23	F	130
12	20	M	150

Anesthetic protocol

Premedication consisted of a combined intramuscular injection of tiletamine HCl and zolazepam HCl (Zoletil 100® Virbac, France) at 1 mg/kg, medetomidine HCl (Sedin®, Vet Farma, Spain) at 0.003 mg/kg (3mcg/kg) and butorphanol tartrate (Butomidor®, Richterharma AG) at 0.05 mg/kg (50mcg/kg). Premedication was administered by distant sedation dart (DAN-INJECT ApS Sellerup Skovvej 116 DK - 7080 Børkop - Denmark) and syringes (arrows) using a 1.2mm x 38mm needle and 1.5ml or 3 ml syringes. An 18G (Neotec Medical Industries Ltd. Singapore) intravenous catheter was placed in both the cephalic and medial saphenous vein. Anesthesia was induced using ketamine HCl (Ketaminol®, Intervet - Holand) at 2 mg/kg administered intravenously into the cephalic vein and an intravenous bolus of propofol (2,6-disopropylphenol) (Norofol® Norbrook, Northern Ireland) at 2 mg/kg administered in the medial saphenous vein, for reasons of chemical incompatibility between propofol and ketamine. A surgical plane of anesthesia was maintained using an intravenous CRI of NaCl 0.9% (10 ml/ kg/h) + ketamine HCl at a rate of 0.8 mg/kg/h and propofol CRI at 0.04 mg/kg/min. All animals were intubated and ventilated with oxygen set at 5-6 L/min. Patients were given intravenous NaCl 0.9% at 10 ml/kg/h while under anesthesia.

Patients were considered under general anesthesia using monitoring of standard anesthetic indicators (corneal eyelids, anal reflex, breathing pattern, heart rate).

Monitoring

The physiological indicators used to monitor patients under anesthesia consisted of rectal temperature, respiratory rate, pulse rate and O_2 sat (%). Hemoglobin oxygen saturation was monitored and recorded using the monitor „MEC 1000 VET" (Mindray Building, Keji 12th Road South, High-tech Industrial Park, Nanshan, Shenzhen 518057, P. R. China). Data points were recorded immediately prior to induction of anesthesia to establish a baseline (0 min. = Baseline), and then in 5 minute increments until 90 minutes post-induction. For personnel safety reasons, monitoring was initiated after premedication was administered.

Research methods

- All parameters were monitored using the patient monitor „MEC 1000 VET" (Mindray Building, Keji 12th Road South, High-tech Industrial Park, Nanshan, Shenzhen 518057, P. R. China)
- Rectal temperature - measured by digital rectal temperature probe
- Respiratory rate - measured using electrodes placed across the thorax. The change in volume during thoracic excursions causes a change in impedance between the electrodes, which is then correlated to a respiratory wave visualized on the monitor
- Sp02 - measured by pulse oximeter placed on patient's the tongue
- Heart Rate - measured by electrocardiogram (ECG)

Statistical analysis

The collected data was analyzed by one-way ANOVA / LSD (Statmost for Windows, DataMost Corp.) to assess the effect of time on the monitored parameters in balanced anesthesia. Differences were considered statistically significant at $p \leq 0.05$ - *, $p \leq 0.01$ - ** , $p \leq 0.001$ - ***

RESULTS

The results of the study are presented in Table 2.

The results confirmed that, in the brown bear (*Ursus arctos*), a balanced anesthetic protocol allows various dental treatments of significant duration with a minimal anesthetic risk for the patient. Respiration remained stable throughout the observation period. Overall results compared to baseline levels did not present statistically significant changes, to the exception of the time point 85 minutes post induction, at which point the respiratory rate was significantly ($p \leq 0.05$) increased to 9 ± 3.5 per minute. The heart rate remained relatively stable throughout the study period.

A statistically significant decrease was observed on the 55th min, where the values reached 42 ± 9.0 per minute at p≤0.05.

Table 2. Respiration rate, heart rate, rectal temperature, and oxygen saturation of arterial hemoglobin of the observed bears

Min.	RR	HR	RT	Sp02
0 min. = Baseline	5±1.5	56±13.5	37.4±0.5	92.3±4.2
5 min	5±1.6	53±10	37.2±0.3	94.2±5.6
10 min	5±1.8	52±10.6	37.1±0.3	93.5±5.4
15 min	5±1.5	51±12.5	36.9±0.4	92.9±3.9
20 min	5±1.5	52±11.0	36.7±0.5**	93.0±3.7
25 min	5±1.4	49±12.7	36.4±0.3***	91.3±7.3
30 min	5±1.9	46±9.7	36.4±0.6**	91.5±7.9
35 min	6±1.4	50±10.8	36.3±0.3**	94.7±3.9
40 min	5±1.8	50±12.3	36.4±0.5**	94.0±4.7
45 min	5±1.7	49±11.8	36.4±0.3*	94.6±3.0
50 min	5±2.1	50±12.5	36.2±0.1***	95±2.7
55 min	5±1.4	42±9.04*	36±0.1***	90.7±5.4
60 min	6±2.0	49±7.04	36.2±0.3*	97.3±1.6*
65 min	4±1.2	46±13.7	36.1±0.4***	95.5±2.3
70 min	6± 1.5	58±6.9	36.3±0.4	91±6.4
75 min	6±1.2	50±7.0	36.1±0.3**	96±4.24
80 min	7±3.69	49±7.	36.0±0.2***	95.5±2.5
85 min	9±3.53 *	49±7.4	36.1±0.2**	95.5±1.4
90 min	6±1.41	55±7.8	36.0±0.3**	92±1.7

Legend: significance of the results compared to baseline values: p≤0.05 - * p≤0.01 - ** p≤0.001 - ***

A statistically significant variation in rectal temperatures was confirmed during the course of this study. We observed a statistically significant decreasing trend in rectal temperatures in almost all observed periods: at 90 min values decreased to 36.0^{O}C ± 0.3 at - p≤0.01.

Data for oxygen saturation of the arterial hemoglobin ($Sp0_2$) remained relatively stable throughout the study. Significant improvement of SpO_2 was measured on the 60th minute. Values were not reported below the lower limits for this species at any time point. Additionally, no vomiting was reported for the patients included in the current study. No salivation was observed and the tongues remained relaxed under anesthesia.

DISCUSSION

The use of a balanced anesthetic protocol using a multimodal pharmaceutical approach allows for lower drug doses and minimization of individual drug-related side effects. Another important advantage of balanced anesthesia is the ability to perform prolonged surgical anesthesia with minimal risks to the patient. It is clearly proven in our results that the use of balanced anesthesia has minimal effects on the main physiological parameters used to monitor anesthesia, despite some fluctuations which for the most part were statistically insignificant.

The results showed relatively stable respiratory activity during the entire study period. Starting with baseline values, a decrease in the respiratory rate is noted (hypopnea) and maintained throughout all studied periods. Moderate hypoventilation has been reported in polar and black bears immobilized with a combination of medetomidine-zolazepam-tiletamine [6,7]. Opposite to polar bears, the use of zolazepam - tiletamine (Zoletil 100® Virbac) in brown bears does not lead to hypopnea [4,6]. The other anesthetic drugs involved in the protocol, such as butorphanol and propofol, have an additional impact on respiratory depression. One of the major side effects of opioids is respiratory depression. Opioids, even administered at low doses may suppress the minute ventilation and increase PaCO2 for 2 to 4 hours [14]. Respiratory depression and even apnea is the most common complication following I.V. administration of propofol [15].

Heart rate remained within reference range at all time points. Consequently balanced anesthesia has a relatively good safety profile regarding its effect on heart rate in the brown bear

The most statistically significant changes in this study were seen in the reported rectal temperatures. A gradual and statistically significant decrease of rectal temperatures was observed at all studied periods, with the lowest values observed on the 90th minute. Bears under anesthesia may react with either a decrease or increase in rectal temperature. Different anesthetics interact in unique ways with the body's thermoregulatory system. Use of opioids can cause hypothermia due to vasodilation. This process is further complicated by the fact that butorphanol directly and dose-dependently influences hypothalamic thermoregulation. Tiletamine and zolazepam in bears usually causes a decrease in rectal temperature [1]. Adding metetomidine to the combination can provoke the opposite effect and increase core temperature [1]. The effects of combining a variety of anesthetics (balanced anesthesia) on the values of rectal temperature have not been studied until now in bears. According to our study results, we can conclude that this anesthetic combination leads to a hypothermic effect in brown bears.

Hypothermia can lead to several negative effects, both during anesthesia and the recovery period. Notably it can blunt the ventilation response to $CO_{2,}$ and a decrease in rectal temperature of 2-3ºC increases the risk of myocardial ischemia, particularly in the postoperative period [16].

Levels of oxygen saturation of the arterial hemoglobin ($Sp0_2$) were maintained within 90 - 100% throughout the study period. Based on these results we can conclude that a balanced anesthesia, despite the presence of respiratory depression and mild hypothermia, does not lead to hypoxia.

CONCLUSIONS

In conclusion, balanced anesthesia is an inexpensive and relatively safe method for various manipulations and procedures in the brown bear. The main physiological parameters are not significantly influenced by the balanced protocol proposed in this study, which can even be used during surgical procedures of short or medium duration. Temperature should however be monitored continuously with this protocol, and respiratory rate observed for bradypnea.

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Authors' contributions

YB and HB participated in the design of the study and performed the statistical analysis, conceived of the study, and participated in its design and coordination and helped to draft the manuscript. ZN participated in the sequence alignment and participated in the design of the study and performed the statistical analysis. BK participated in the design of the study and performed the statistical analysis. MG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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FIZIOLOŠKI EFEKTI BALANSIRANE ANESTEZIJE TOKOM STOMATOLOŠKE INTERVENCIJE KOD MRKIH MEDVEDA (*URSUS ARCTOS*)

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Cilj studije je bio praćenje fizioloških efekata standardizovanog balansiranog protokola anestezije kod mrkih medveda (*Ursus arctos*) tokom rutinskih stomatoloških tretmana. Fiziološki parametri (rektalna temperatura, puls, respiracija i saturacija kiseonikom) su posmatrani na uzorku od 12 mrkih medveda koji su boravili u okviru parka koji se nalazi u Belitzi (Bugarska). Životinje su anestezirane u periodu od 90 minuta, izbalansiranom kombinacijom anestetika. Premedikacija se sastojala iz intramuskularne aplikacije tiletamina CHl i zolazepama HCl (Zoletil 100, Virbac, Francuska) 1,0 mg/kg telesne mase, medetomidina HCl 0,003 mg/kg telesne mase i 0,05 mg/kg telesne mase butorfanola. Anestezija je obavljena intravenski sa kombinovanim bolusom ketamina (2,0 mg/kg telesne mase) i propofola (2,0 mg/kg telesne mase). Održavanje anestezije je obavljeno infuzijom ketamina (0,8mg/kg/sat) i propofola (0,04 mg/kg/min). Rektalna temperatura je značajno opala tokom trajanja anestezije dok su puls, frekvencija disanja i saturacija kiseonikom bili stabilni, bez značajnih promena ovih parametara, tokom trajanja anestezije. Na osnovu rezultata, može da se zaključi da je kombinacija navedenih preparata podesna za primenu u navedenom vremenskom periodu tokom stomatoloških intervencija kod mrkih medveda.