pISSN 1598-298X / eISSN 2384-0749
J Vet Clin 36(6) : 306-313 (2019)
http://dx.doi.org/10.17555/jvc.2019.12.36.6.306

Journal of Veterinary Clinics
www.ksvc.or.kr

Comparison of Anesthetic Responses Induced by MZT and XZT Combinations at General Anesthesia for Laparoscopic Salpingectomy in Rearing Female Asiatic Black Bears (*Ursus thibetanus*)

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(Received: October 28, 2019 / Accepted: November 20, 2019)

Abstract : It is important to identify the most suitable anesthetic agent that has minimal side effects to be able to control and perform surgeries on bears. In this study, we examined and compared the induction and recovery times as well as the physiological changes occurring during anesthesia induced by medetomidine-zolazepam/tiletamine (MZT) and xylazine-zolazepam/tiletamine (XZT) at general anesthesia for laparoscopic salpingectomy in 326 female Asiatic black bears. The body temperature, heart rate, respiratory rate, and levels of PaO_2 and $EtCO_2$ were the physiological changes measured during surgical procedures in female bears after anesthesia. In addition, the levels of pO_2, pCO_2, and sO_2 were measured using a portable blood gas analyzer. To induce recovery from anesthesia, bears anesthetized with MZT were intravenously administered atipamezole and bears anesthetized with XZT were intravenously administered yohimbine. The combination MZT, at dosages of 0.019 ± 0.001 mg/kg for medetomidine and 1.4 ± 0.1 mg/kg for ZT, or the combination XZT, at dosages of 2.0 ± 0.1 mg/kg for xylazine and 3.0 ± 0.1 mg/kg for ZT, proved to be reliable and effective in anesthetizing Asiatic black bears for a 40-min handling period for routine clinical procedures. The average anesthesia induction times were 16.5 ± 0.95 min for the bears in the MZT group and 12.0 ± 0.44 min for those in the XZT group. A significant difference was noted between the two drugs ($P < 0.001$) in terms of the average anesthesia induction time. The anesthesia induction time was shorter for bears with lower body weights than those with higher body weights ($P < 0.05$). The recovery time of MZT was significantly faster than that of XZT (11.3 ± 0.45 min vs. 18.5 ± 0.83 min) ($P < .001$). The bears anesthetized with MZT exhibited lower cardiopulmonary suppression than those anesthetized with XZT ($P < 0.05$). The body temperatures and $EtCO_2$ of bears in the MZT group were significantly lower than those in the XZT group as time progressed after anesthesia ($P < 0.05$). The average pO_2 before the bears were supplied with oxygen was 64.8 ± 3.7 mmHg, but it increased to 211.5 ± 42.5 mmHg afterwards ($P < 0.001$). In conclusion, our results indicate that bears anesthetized with MZT have longer anesthesia induction time, shorter recovery time, slower heart and respiratory rates, and lower body temperatures and $EtCO_2$ than those anesthetized with XZT. These findings suggest that XZT is preferable to MZT, warranting further research on its uses and clinical responses in bears.

Key words **:** anesthesia, Zoletil®, medetomidine, xylazine, rearing Asiatic black bear.

Introduction

There are eight species of bears across the world, including the giant pandas (8). One of the species, the Asiatic black bear (*Ursus thibetanus*), is distributed throughout Afghanistan, Pakistan, India, China, Indochina, Russia, Taiwan, Korea, and Japan (32). In the entire South Korea region, there are only about 20 Asiatic black bears (half-moon bears) concentrated in the Jirisan area and less than 10 bears in the Jirisan National Park (18). In contrast, several hundred bears are raised to produce bile on farms (24).

The extraction of bile from bears is an act of animal abuse that has received international criticism as it involves the killing of the bears (33,35,38). Several international organizations, public bodies, and governmental and environmental groups have raised questions about the ethicality of breeding bears in farmhouses. In response, the government decided to sterilize all captive-bred bears between 2014 and 2016 to prevent the breeding of bears in the farms (28,29). The bears included in this study were bred in a farmhouse. Initially, captive bears were imported from other countries. Considering the limited literature on anesthesia in bears, it was deemed important to evaluate different anesthetics while studying bears and performing surgical procedures on them (15,30).

As bears are wild and dangerous animals, most researchers avoid the use of drugs such as propofol and other mild anesthetics. Instead, general anesthesia, through the use of a blowgun or gas-pressurized dart for its administration, is rec-

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ommended (5). Determination of the anesthetic agent dosage is important to be able to perform successful surgeries. For wild animals, anesthesia must preferably be achieved on the first attempt, unlike the case for trapped animals wherein several attempts are possible. However, it is always preferable to use appropriate doses to ensure the minimum amount of injection punctures to avoid inflicting wounds that negatively influence the animal's welfare. Once the appropriate dose is established, the final dose of the drug to be administered may be adjusted as required (6).

When anesthetizing a bear, safe anesthetics causing less adverse effects to the health and wellbeing of the animal should be selected (26). Because known anesthetic drugs acting on the central nervous system cause cardiopulmonary function suppression in different ways, the use of more than one agent is recommended to diminish risks. Wildlife handlers should select anesthetics and adopt protocols that ensure safety for humans and minimize adverse effects for the animals. Various anesthetic methods have been designed for inducing anesthesia in bears (1,4,6,7,13,16,19-21,27,36,37,39). For many years, the combination of zolazepam and tiletamine (ZT) has been used at a 1:1 ratio to anesthetize bears (4,6,36,39). ZT alone can be administered safely in large doses, but the lack of an antagonist results in long recovery times that discourage the use of this combination alone (5,6). The combined administration of ZT and an α_2-agonist drug has been studied (1,6,7,9,16,20,27,37). For example, medetomidine or xylazine have been used in combination with ZT and found to be effective in anesthetizing polar, grizzly, Japanese black, and black bears (1,3,4,6,9,22). The use of medetomidine in combination with ZT (medetomidine-zolazepam-tiletamine; MZT) is advantageous as it reduces the dose of ZT and allows for relatively fast recovery upon administration of an antagonist such as atipamezole (6).

In addition, the combined administration of the $\alpha_{1,2}$-agonist xylazine and ZT (xylazine-zolazepam-tiletamine; XZT) is inexpensive and helps reduce the volume of ZT by one-third. However, hyperthermia and hypoxemia have been noted with its use during anesthesia (5,31). The dose of ZT is restricted to a maximum of 2.8-4.4 mg/kg in Asiatic black bears (8,10). In addition, for long-lasting anesthesia, a combination of medetomidine and ZT is useful as it induces anesthesia through inhalation, which can be easily regulated (21).

The anesthetic dosage for effective anesthesia in bears varies with the bear species. The optimal dose of medetomidine has been established at 0.02-0.06 mg/kg for brown bears (13), 0.04 mg/kg for Japanese black bears (22), and 0.03-0.045 mg/kg for Asiatic black bears (20). However, as medetomidine is sold at 1 mg/kg, its use in large animals is limited by the limited commercial availability of concentrated Domitor® solution (26). In contrast, xylazine is commercially available as high concentrated solutions, and it is easy to prepare appropriate large doses. The optimal XZT dosage is a combination of xylazine and ZT in a 2:3 ratio (3,5).

Despite the abundance of literature on MZT use in polar, brown, and Japanese black bears, there are only limited reports on the appropriate dosages and physiological changes in Asiatic black bears (19,20). In addition, no studies have compared the use of MZT and XZT for inducing anesthesia for laparoscopic salpingectomy in rearing Asiatic black bears. Therefore, the present study aims to determine the optimal anesthetic doses of MZT and XZT, compare the induction and recovery times when using the two different drug combinations, and provide data on the physiological changes occurring during anesthesia induced by MZT and XZT for laparoscopic salpingectomy in rearing female Asiatic black bears.

Materials and Methods

Study area and animals

From April to May 2015, a total of 326 rearing female Asiatic black bears (326 female bears) were anesthetized for surgical treatment (laparoscopic salpingectomy). These procedures were performed in 32 bear farms in South Korea (location: 34°56′-38°35′N, 126°31′-129°22′E). In these farms, the bears were kept in a large captive pen with a cement- or steel-barred floor. The animals were fed a mixture of acorns, vegetables, breads, and a commercial feed twice a day. Water was always available.

Anesthetic procedures

The bears were fasted for more than 24 h before anesthesia. Initially, the anesthetic agent doses were calculated by grossly estimating the body weight of each bear. The anesthetic was administered by darting using a blowgun. MZT or XZT was used for the anesthesia. The dosages of MZT and XZT were prepared (5 mL/100 kg of body weight). A total of 86 bears were anesthetized with MZT consisting of 40.0 μg/kg medetomidine (Domitor®; Orione, Espoo, Finland) and 2.0 mg/kg ZT (Zoletil 50®; Virbac SA, France). The mixed solution contained approximately 0.8 mg/mL of medetomidine and 40.0 mg/mL of ZT. A total of 240 bears were anesthetized with XZT. XZT consisted of 2.0 mg/kg xylazine (Xyzine®, 100 mg/kg; SF, Ansan, Korea) and 3.0 mg/kg Zoletil® (at a 2:3 combination ratio). The mixed solution contained approximately 34.7 mg/mL of xylazine and 52.1 mg/mL of ZT (for a final volume of 4.8 mL/vial).

The anesthesia procedure was performed by grossly estimating the body weight of each bear, calculating an appropriate volume for the anesthetic agent, and darting the animal with an anesthetic-charged blowgun. The anesthesia induction was deemed complete by examining the bears for lack of responses to stimulation upon arms or head lifting after the darting event. The times from darting to the completion of the anesthesia induction were recorded. After anesthesia induction, the bears were blindfolded and transported to the operating room on a cart for their surgical treatment. In the operating room, the bears were weighed on an electronic balance. Next, they were restrained on an operating table, tilted down at a 10° angle by placing them in a foot-up and head-down position in dorsal recumbency, followed by intubation with a 10 mm endotracheal tube equipped with an inflatable cuff to supply 100% oxygen.

After the completion of all procedures in the operating room, the bears were moved to the recovery room, and then atipamezole (Antisedan®; Orion, Espoo, Finland), a medetomidine antagonist, was intravenously administered using an

Table 1. Body weight, dose of zolazepam-tiletamine (ZT) and premedication for anesthetic induction, and the total volume in 326 rearing female Asiatic black bears immobilized with medetomidine-zolazepam/tiletamine (MZT) or xylazine-zolazepam/tiletamine (XZT)

Group	n	Body weight (kg)	ZT dose (mg/kg)	Dose of premedication (mg/kg)	Total volume (mL)
MZT	86	63.2 ± 1.8[a] (27-156.6)	1.4 ± 0.1[a] (0.4-4.5)	0.019 ± 0.001 (0.005-0.06)	3.0 ± 0.2[c] (0.6-8.5)
XZT	240	68.8 ± 1.6[b] (15-221)	3.0 ± 0.1[b] (0.9-9.3)	2.0 ± 0.1 (0.6-7.3)	3.3 ± 0.1[d] (0.5-10.0)

[a,b] $P < 0.05$, [c,d] $P < 0.0001$.

equivalent medetomidine dose. Otherwise, yohimbin (Xyverse®; SF Co., Ansan, Korea), a xylazine antagonist, was administered intravenously at a dose similar to that of the initial xylazine. The times from darting to the injection of the antagonist was also recorded. The bears were then left to recover from anesthesia in a lateral recumbency position.

Monitoring

The anesthetized bears were monitored using a patient monitor (DN5; BioNet, Korea). For electrocardiograms, electrodes were attached to both the axillary portions of the animal's forelimb and the inner skin of the left thigh. A temperature probe was inserted into the esophagus to measure body temperature. The SpO_2 sensor was attached to the animal's tongue. The anesthetized bears were allowed to breathe spontaneously while the patient monitoring system recorded the heart rate, the respiratory rate, the esophageal temperature, the SpO_2, and the $EtCO_2$. For each bear under observation we recorded the times for anesthesia induction, anesthesia, operation, and recovery (darting time, anesthesia completion time, the start and end time of the surgical procedure, head-lifting time, and sternal recumbency time).

Glucose and blood gas analyses

Blood was collected from the femoral artery of the animals for their blood gas analysis before (n = 27) and after (n = 19) supplying them with oxygen. The collected blood samples were analyzed with a point of care device (i-STAT® handheld; Abbott Point of Care, NJ, USA). And, $CG8^+$-cartridges were used for the analyses of partial pressure of oxygen (pO_2), oxygen saturation (sO_2), partial pressure of carbon dioxide (pCO_2), standard bicarbonate (HCO_3), pH, and the levels of glucose, hematocrit (Hct), hemoglobin (Hb), sodium (Na), potassium (K), and ionized calcium (iCa). The analyses were conducted immediately after the blood collection, and all of them were performed under similar conditions.

Biochemical analyses

Blood was collected from the femoral or the jugular veins for blood biochemistry analysis. The blood samples were centrifuged within 2 h of their collection, and the serum was separated and stored in an icebox at 4°C, followed by transfer to the laboratory for cryopreservation. The alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities, and the levels of blood urea nitrogen (BUN), creatinine, albumin, sodium, potassium, chloride, and glucose were measured by an automatic blood analyzer (serum biochemistry: Hitachi 7202, Hitachi High-18 Technologies, Tokyo, Japan; electrolyte analyses: HumaLyte, HUMAN Gesellschaft fur 19 Biochemica und Diagnostica, Wiesbaden, Germany).

Statistical analyses

All data obtained were expressed as mean ± standard error of the mean. Statistical analyses were performed using the SAS program (version 9.4 SAS Inst., Cary, NC, USA). The general linear model procedure was applied to compare the anesthesia induction times and the anesthesia recovery times between the bears in both anesthetic groups (MZT vs. XZT), and between body weight groupings (< 63 vs. ≥ 63 kg). The ZT doses, pre-anesthetic doses, and the total volumes of the anesthetic agents were compared between the MZT and XZT groups by using the Student's t-test. Also, the changes in heart rates, respiratory rates, body temperatures, and $EtCO_2$ during anesthesia were compared between the two anesthetic groups by using the Student's t-test. $P < 0.05$ was considered to be statistically significant.

Results

The data on the body weights and gender of the bears, the doses of ZT required for anesthetic induction, doses of premedication, and the total volume of anesthetics in the MZT and XZT groups are summarized in Table 1. The body weights of the animals were smaller in the MZT than in the XZT group bears ($P < 0.05$). The doses of medetomidine and ZT used to induce anesthesia in the MZT group were 0.019 ± 0.001 mg/kg and 1.4 ± 0.1 mg/kg, respectively. The highest dose of medetomidine was 60.0 μg/kg, which is three-times the mean dose, whereas that of ZT was 4.5 mg/kg, which is three-times the dose of the medication. The doses of xylazine and ZT were 2.0 ± 0.1 mg/kg and 3.0 ± 0.1 mg/kg, respectively. The highest dose of xylazine was 7.3 mg/kg and that of ZT was 9.3 mg/kg. However, no adverse effects from

Table 2. Comparative evaluation of induction and reversal times according to body weight, and anesthetics in 326 rearing female Asiatic black bears receiving either medetomidine-zolazepam/tiletamine (MZT) or xylazine-zolazepam/tiletamine (XZT)

Variables	n	Induction time (min)	Reversal time (min)
Anesthetics			
MZT	86	16.5 ± 0.95[a]	11.3 ± 0.45[a]
XZT	240	12.0 ± 0.44[b]	18.5 ± 0.83[b]
Body weight (kg)			
< 63	172	11.7 ± 0.7[e]	14.8 ± 0.9[e]
≥ 63	154	14.4 ± 0.6[f]	17.9 ± 0.9[f]

[a,b] $P < 0.001$; [c,d] $P < 0.05$; [e,f] $P < 0.05$.

Table 3. Glucose and arterial blood gas results before and after oxygen supplementation in rearing female Asiatic black bears anesthetized with medetomidine-zolazepam/tiletamine or xylazine-zolazepam/tiletamine

Variables	Oxygen supply	
	Before (n = 27, Range)	After (n = 19, Range)
pO_2 (mmHg)	64.8 ± 3.7 (27-91)[a]	211.5 ± 42.5 (35-545)[b]
sO_2 (%)	87.2 ± 2.6 (44-97)	93.2 ± 2.6 (58-100)
pCO_2 (mmHg)	35.3 ± 0.9 (27.9-39.6)[c]	39.5 ± 1.7 (32.2-53.7)[d]
HCO_3 (mmol/L)	19.4 ± 0.3 (17.4-21.3)	20.5 ± 0.6 (17.0-23.6)
pH	7.35 ± 0.01 (7.29-7.42)	7.33 ± 0.01 (7.25-7.40)
Glucose (mg/dL)	91.5 ± 2.8 (75-101)[e]	110.8 ± 5.1 (76-148)[f]

pO_2; partial pressure of oxygen, sO_2: oxygen saturation, pCO_2: partial pressure of carbon dioxide, HCO_3: standard bicarbonate.
[a,b] $P < 0.001$; [c,d] $P < 0.01$; [e,f] $P < 0.05$.

the anesthetic agents were noted. The total volume for induction of anesthesia was 3.0 ± 0.2 mL for the MZT group, and 3.3 ± 0.1 mL for the XZT group, with a significant difference ($P < 0.0001$) between the groups.

Table 2 compares the anesthesia induction and recovery time of between the two anesthetic agents used. The average anesthesia induction times were 16.5 ± 0.95 min for MZT and 12.0 ± 0.44 min for XZT, suggesting that XZT had significantly shorter induction times than MZT ($P < 0.001$). The anesthesia recovery times were 11.3 ± 0.45 min for MZT and 18.5 ± 0.83 min for XZT; thus, significantly shorter for MZT than for XZT ($P < 0.001$). And, with reference to the body weights, the anesthesia induction and recovery times were shorter for bears weighing < 63 kg than for bears weighing ≥ 63 kg ($P < 0.05$).

Table 3 shows the results of the measurement of oxygen saturation, carbon dioxide saturation and blood glucose concentration before and after supplying oxygen to the female bears anesthetized with MZT and XZT. We found an average oxygen partial pressure of 64.8 ± 3.7 mmHg before the oxygen supply and of 211.5 ± 42.5 mmHg after it ($P < 0.001$). The carbon dioxide partial pressure was 35.3 ± 0.9 mmHg before the oxygen supply and 39.5 ± 1.7 mmHg after it ($P < 0.01$). Additionally, the concentration of glucose after the oxygen supply was higher than it was before the supply ($P < 0.05$).

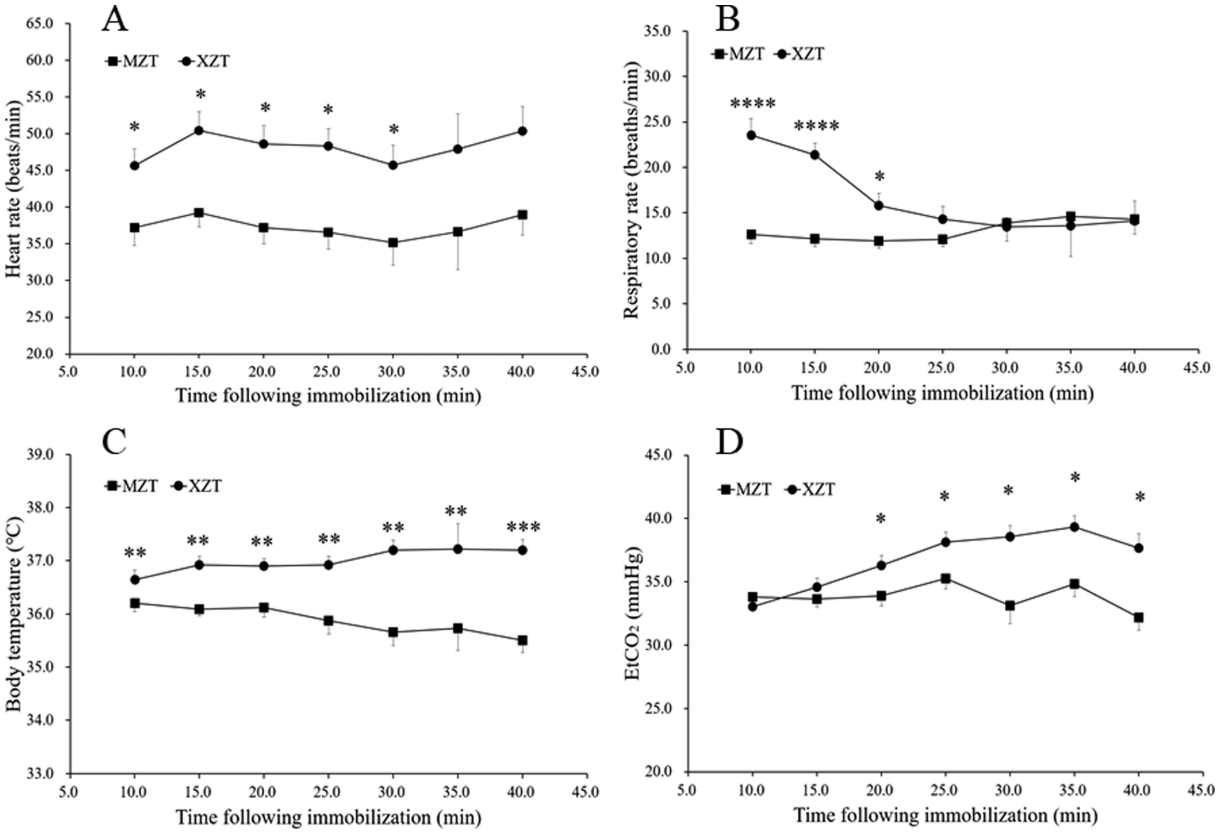

Fig 1. Changes in the mean ± SEM heart rate (A), respiratory rate (B), body temperature (C), and $EtCO_2$ (D) values in rearing Asiatic black bears anesthetized with medetomidine-zolazepam/tiletamine (MZT) or xylazine-zolazepam/tiletamine (XZT). * $P < 0.05$, ** $P < .01$, *** $P < 0.001$, **** $P < 0.0001$.

Table 4. Profiles of blood chemistry before surgical treatment in 326 rearing female Asiatic black bears anesthetized with medetomidine-zolazepam/tiletamine (MZT) or xylazine-zolazepam/tiletamine (XZT)

Variables	Unit	MZT (n = 86)	XZT (n = 240)
ALP	IU/L	62.0 ± 4.7[a]	57.8 ± 3.7[b]
ALT	IU/L	13.7 ± 0.6	17.3 ± 1.4
Albumin	g/dL	3.5 ± 0.1	3.4 ± 0.1
BUN	mg/dL	16.7 ± 1.0[a]	11.3 ± 0.5[b]
Creatinine	mg/dL	1.9 ± 0.1	1.5 ± 0.1
Glucose	mg/dL	70.7 ± 2.4[a]	81.7 ± 2.0[b]
Sodium	mmol/L	139.3 ± 1.3	144.6 ± 1.0
Potassium	mmol/L	4.3 ± 0.1	4.6 ± 0.1
Chloride	mmol/L	104.7 ± 0.7	107.9 ± 0.8

ALP: alkaline phosphatase, ALT: alanine aminotransferase, BUN: blood urea nitrogen. [a,b] $P < 0.001$.

The result of blood biochemistry tests for the two groups was as follows (Table 4): the serum levels of ALP and BUN were higher in the MZT group than in the XZT group ($P < 0.001$), but the glucose levels were lower in the MZT group than in the XZT group ($P < 0.001$). The results of other blood chemistry variables did not show any significant differences between the two groups.

Bears anesthetized with XZT recorded faster heart rates at around 10-30 min after the initiation of anesthesia as compared to those anesthetized with MZT ($P < 0.05$), but no significant differences were observed after 35 min (Fig 1A).

The bears anesthetized with XZT showed significantly higher respiratory rates than those anesthetized with MZT until 15 min after the initiation of anesthesia ($P < 0.0001$). Significant differences were noted until after 20-min of initiation inclusively ($P < 0.05$). But, thereafter, no significant difference was observed between the two groups (Fig 1B).

We recorded higher body temperatures in bears anesthetized with XZT than in those anesthetized with MZT ($P < 0.01$) (Fig 1C). With time, the recorded body temperature gradually increased in the XZT group and gradually decreased in the MZT group, with significantly different values between the two groups noted at 40 min after anesthesia initiation ($P < 0.001$).

Fig 1D reveals the partial pressures of carbon dioxide in the MZT and XZT group bears according to the time elapsed after anesthesia initiation. The average carbon dioxide partial pressure was significantly higher in the XZT group than in the MZT group bears ($P < 0.05$) at 20 min after the anesthesia initiation and remained so until the end of the anesthesia.

Discussion

Anesthesia is a critical requirement for the care, management, and treatment of bears, and diverse anesthetic methods have been tested (1,4,6,7,13,16,19-21,27,36,37,39). The establishment of an effective and safe anesthetic protocol for wild animals is important to ensure the safety of both the animal under observation and the operators (11,14). In addition, depending on the method of capture, the amount of effective and safe dose must be established prior to the procedure (11). In this study, reared female Asiatic black bears were effectively anesthetized with MZT and XZT.

When rearing Asiatic black bears dosages of 2.8-4.4 mg/kg of ZT produce efficient and safe animal immobilization. But, the lack of a suitable antagonist can result in prolonged recoveries for the anesthetized animals (2,22). A combination of ZT with an $\alpha_{1,2}$-agonist was proposed in previous publications in order to reduce the dose of ZT and shorten the recovery time (5,13,14,20). Possible pre-anesthetic agents for use in combination with ZT include medetomidine, xylazine, acepromazine, and butorphanol tartrate (1,4-6,9,22). Medetomidine and xylazine have been the most commonly used drugs for this purpose (4,20,31). In this study, we evaluated the dosage of both drug combinations, their time for induction and recovery, and the physiological responses after anesthesia induction.

We found that the combination of 0.019 mg/kg medetomidine and 1.4 mg/kg ZT (used in the MZT bear group), and the combination of 2.0 mg/kg xylazine and 3.0 mg/kg ZT (used in the XZT bear group) both achieved effective anesthesia. No side effects were detected with either anesthetic combination. The dose of medetomidine in MZT combination has been set at 40 μg/kg for Japanese black and brown bears, 75 μg/kg for polar bears, and 52 μg/kg for black bears (6,8). Moreover, Jeong *et al.* (20) have used a medetomidine dosage of 0.03-0.045 mg/kg in Asiatic black bears, whereas others have reported different dosages.

In this study, all of the bears receiving more than thrice the dose of MZT and XZT recovered safely from anesthesia and thus their experiences confirm the safety of these anesthetic agents. This result agrees with a report that guaranteed the safety of XZT even with doses 2 to 3 times the recommended dose for grizzly bears (5). The efficient dose for bears has been reported to differ by season, probably due to differences in the animal's health status (8,34). A ratio of 2:3 in bears administered xylazine and ZT has been shown to be the most efficient with respect to the times for induction and recovery from anesthesia (5). We prepared our anesthetics using the same 2:3 ratio; and a total of 326 bears underwent complete surgical procedures without any adverse events resulting from anesthesia.

For anesthetizing wild animals, the final dose is extremely critical and it should be decided based on the environmental conditions (wild state versus captured state). In captured animals, more than one anesthetic agent can be used until complete anesthesia is achieved. But, for animals in the wild, a high concentration of anesthetics is necessary because anesthesia must optimally be performed with a single darting. In this study, the heaviest bears weighed about 220 kg, and the established dose of the drug had to be administered in 5 mL, which resulted in the use of two darts for inducing anesthesia. However, some bears were administered up to five times that volume because of individual differences in their overall response to the drug. Currently, medetomidine is commercially available in a dose of 1 mg/mL, but it is possible to obtain higher concentrations from the provider, and detomidine at 10 mg/mL has been used (26). Xylazine is commercially available at various concentrations (e.g., 100 and 300 mg/mL), and the required concentration of xylazine is more

easy to obtain. For this study, we used a formulation containing xylazine at 100 mg/mL (Xyzine®). We also used Zoletil 50®, and left the preparation of Zoletil 100® for occasions in which a high-concentration preparation was mandatory.

The average anesthetic induction time that allowed for surgical performance after administration of the anesthetic agent was faster for XZT (12.0 min) than for MZT (16.5 min). Our results are consistent with those of earlier studies reporting MZT induction times at 16 min and 16.6 min, in brown and Asiatic black bears (13,26), and slightly delayed compared with the 13.7 min reported in another study (20). The reported anesthesia induction times of XZT at 4.1 min for polar bears and 6.2 min for grizzly bears (3) were faster than that in our study (5). And, the differences in the induction times observed between grizzly and polar bears were thought to be caused by overestimation of grizzly bears' weights (5). In our case, we calculated the anesthetics dose administered averaged 5 mL/100 kg (2 mg/kg for xylazine, and 3 mg/kg for ZT), which indicates that we used relatively lower anesthetics concentrations.

The recovery time, calculated from the administration of the reversing agent to the moment the bear regains movement, has a great influence on the overall wellbeing and vulnerability to risks in bears. We observed a faster average recovery time in the MZT group (11.3 min) than in the XZT group (18.5 min) ($P < 0.001$) and evidenced faster recovery times for male bears than female bears. Also, lightweight bears showed faster recovery than the heavier ones ($P < 0.05$). The average anesthesia recovery time in our MZT group (11.3 min) was shorter than that of medetomidine and ZT (25.3 min) for Asiatic black bears reported elsewhere (26). And, the anesthesia recovery time in our XZT group was similar to that reported in grizzly bears (19.7 min) (5), but shorter than that in polar bears (33.9 min) (3). These differences may be attributed to differences in the establishment of criteria for recovery from anesthesia.

The recovery signs used in our study included chewing, tongue movements, and licking. The sequence of behaviors during the recovery period consists of head lifting, followed by sternal recumbency, and finally sitting. After that, the animal usually proceeds to standing up and moving about (26). In this study, the recovery time was measured as the time from α_2-antagonist administration to the time of sitting up on sternal recumbency. The induction and recovery times of anesthesia were faster in male bears than in female bears, probably due to the physiological activation of the female bear at the onset of the estrus period (23). Seasonal differences have been reported to affect the anesthesia induction and recovery times (13).

In bears, MZT and XZT anesthesia can induce hypoxemia, because they suppress the cardiopulmonary function. Moreover, the carbon dioxide used in laparoscopic surgery can be absorbed from the abdominal cavity and cause hypercapnia. The subjects of this study were supplied with oxygen through intubation to prevent hypercapnia during laparoscopic salpingectomy. We found the oxygen saturation was significantly increased ($P < 0.001$) after supplying oxygen, and the carbon dioxide partial pressure was also significantly elevated ($P < 0.01$). Our results support previous reports that oxygen supply for hypoxemia prevention is necessary in these cases (5,31). We also found the serum glucose concentration increased significantly after supplying oxygen ($P < 0.05$; Table 3). This increase has been reported, and medetomidine and xylazine are thought to act on α_1-adrenergic receptors to increase glucose production from the liver and on α_2-adrenergic receptors to inhibit the release of insulin into the blood (17,25).

Anesthetic agents suppress the cardiopulmonary function. Our bears anesthetized with MZT showed significantly slower heart rates than those anesthetized with XZT (Fig 1A). During the anesthesia period, we recorded heart rates of < 40 beats/min for bears anesthetized with MZT, and of > 45 beats/min for those anesthetized with XZT, indicating that MZT has a stronger cardiac suppressing effect than XZT. Our result was similar to that of a report wherein the average heart rate was 51 beats/min in Asiatic black bears (20) and ranged from 40-70 beats/min in grizzly bears (5). But, our average heart rate findings differed from another report wherein the average heart rate for ZT was 60 beats/min and that of XZT was > 90beats/min (5). Bears anesthetized during the winter season show a significantly lower heart rate than those anesthetized during the summer (13), and since our study was conducted during the spring season, the difference in heart rate results may be attributed to seasonal variation.

We found the average respiratory rate in the XZT group to be significantly higher than that in the MZT group until 20 min after anesthesia (Fig 1B). Thereafter, the bears in both groups showed similar respiratory rates. Our results are similar to those wherein brown bears and Asian black bears had heart rates ranging between 11 and 14 beats/min until up to 1 hr after anesthesia with MZT (14,20). However, we detected an increase in the respiratory rate at the beginning of anesthesia in the XZT group, which resonates with the reports of other investigators (3,14,22). Further studies are warranted to determine the cause of these respiratory rate increases.

The body temperature was significantly higher in bears anesthetized with XZT than in those anesthetized with MZT (Fig 1C). The temperature increased gradually over time after XZT anesthesia, whereas temperature decreased gradually in bears administered MZT. These results are consistent with previous reports of hyperthermia after XZT anesthesia in polar bears and grizzly bears (3,5). Although xylazine is a known $\alpha_{1,2}$-adrenergic agonist that can increase body temperature by participating in peripheral vasoconstriction and capillary thermoregulation (3,12,25), the way in which xylazine increases the body temperature remains unknown. Among grizzly bears anesthetized with MZT, those anesthetized in winter have a lower body temperature as compared to those anesthetized during summer (13). After anesthesia induction, the body temperature has been seen to increase in the winter and decrease in the summer (13). Our study was conducted in the spring and we evidenced comparatively intermediate temperature values between those reported for the winter and summer seasons. Thus, body temperature changes at the time of anesthesia are influenced by the environmental temperature, and administration of MZT anesthesia during the summer helps reduce the occurrence of hyperthermia. We did not see evidence of adverse events after MZT

administration to the bears, and can confirm its safety as no animal deaths occurred with the use of the two anesthetic agents.

In conclusion, MZT (the combination of 0.019 mg/kg medetomidine and 1.4 mg/kg ZT) and XZT (the combination of 2.0 mg/kg xylazine and 3.0 mg/kg ZT) both proved to be reliable and effective for inducing anesthesia in Asiatic black bears. In addition, our results revealed that bears anesthetized with MZT experienced longer induction times, shorter recovery times, slower heart and respiratory rates, and lower body temperatures and $EtCO_2$ than bears anesthetized with XZT.

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