

## RESEARCH PAPER

## Evaluation of BAM (butorphanol–azaperone–medetomidine) in captive African lion (*Panthera leo*) immobilization

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### Abstract

**Objective** The combination of butorphanol, azaperone and medetomidine (BAM) with subsequent antagonism by naltrexone–yohimbine or naltrexone–atipamezole was evaluated for reversible immobilization of captive African lions (*Panthera leo*).

**Study design** Prospective, clinical trial.

**Animals** Twenty lions, 11 males and nine females, weighing 38–284 kg were immobilized in South Africa.

**Methods** The BAM volume dose rate administered was 0.005–0.008 mL kg<sup>-1</sup> (0.6 mL 100 kg<sup>-1</sup>). Physiologic variables were recorded every 5 minutes. Four arterial blood samples were collected from all animals at 20, 30, 40 and 50 minutes after immobilization for analysis of blood-gases and acid-base status.

**Results** The actual doses administered were as follows: butorphanol, 0.18 ± 0.03 mg kg<sup>-1</sup>; azaperone, 0.07 ± 0.01 mg kg<sup>-1</sup>; and medetomidine, 0.07 ± 0.01 mg kg<sup>-1</sup>. The inductions were calm and smooth, and induction time ranged from 4 to 10 minutes (7 ± 2 minutes). The amount of time needed to work with each lion was 70 minutes, and no additional drug doses were needed. Heart rate (40 ± 8 beats minute<sup>-1</sup>) and respiratory frequency (15 ± 4 breaths minute<sup>-1</sup>) were stable throughout immobilization. The mean arterial

blood pressure of all animals was stable but elevated (142 ± 16 mmHg). The rectal temperature slightly increased over time but remained within acceptable range. The recovery time was significantly shorter when using naltrexone and atipamezole (9 ± 1 minutes) compared to using naltrexone and yohimbine (22 ± 7 minutes).

**Conclusion and clinical relevance** The BAM combination proved to be reliable for general veterinary anaesthesia in lions. During anaesthesia, minor veterinary procedures such a blood collection, intubation, vaccination and collaring could safely be performed with no additional dosing required.

**Keywords** azaperone, BAM, butorphanol, lion, medetomidine.

### Introduction

African lions (*Panthera leo*) are often immobilized for routine procedures such as microchipping, collaring, disease prevention and medical treatment. These immobilizations require the use of drugs that are safe, not only for the animals but also for the people working with them (i.e., induce a deep plane of anaesthesia) since lions are notoriously aggressive and dangerous.

Traditionally, dissociative anaesthetics (ketamine and tiletamine) combined with relatively small concentrations of sedative and tranquilizing medications

(xylazine, medetomidine, detomidine) are applied for the anaesthesia of lions (Fahlman et al. 2005; Jacquier et al. 2006; Fyumagwa et al. 2012). Combinations of ketamine–xylazine and tiletamine–zolazepam–medetomidine are considered to be the most suitable combinations (Herbst et al. 1985; Fahlman et al. 2005; Jacquier et al. 2006). The application of all the above-mentioned combinations has both advantages and disadvantages (Herbst et al. 1985; Tomizawa et al. 1997; Fahlman et al. 2005; Jacquier et al. 2006; Fyumagwa et al. 2012; Kreeger & Arnemo 2012). More recently, a combination of butorphanol, medetomidine and midazolam (BMM) has been successfully used in free-ranging lions for a period of 45 minutes (Wenger et al. 2010).

BAM (the combination of butorphanol–azaperone–medetomidine), as described in this article, is a dry mixture, containing 300 mg of butorphanol tartrate, 120 mg of azaperone tartrate and 120 mg of medetomidine hydrochloride. The use of this combination has been reported in species such as white-tailed deer (*Odocoileus virginianus*) (Mich et al. 2008; Miller et al. 2009; Siegal-Willott et al. 2009), rocky mountain elk (*Cervus elaphus nelsoni*) (Wolfe et al. 2014), Nubian ibex (*Capra nubiana*) (Lapid & Shilo-Benjamin 2015), bighorn sheep (*Ovis canadensis*) (Smith et al. 2014) and black bear (*Ursus americanus*) (Wolfe et al. 2008). It has been reported to produce reversible anaesthesia without hyperthermia and good analgesia. In addition, it can be delivered with a low-volume dart (Lance 2008). One disadvantage noted in cervids is that this combination may result in significant hypoxia, and oxygen supplementation is recommended (Mich et al. 2008; Miller et al. 2009; Siegal-Willott et al. 2009).

To our knowledge, this is the first time that this combination has been used as a ready-made medication for the immobilization of a felid species, specifically lions. The aims of this study were to acquire comprehensive and reliable monitoring data as well as develop, explore and describe the use of BAM for the immobilization of captive African lions.

## Materials and methods

### Animals, medications and delivery methods

Twenty lions (11 males and nine females) were immobilized with BAM on the Lechwe Lodge private game farm in the Free State province (August 2014; 13 lions) and at Moholoholo Wildlife Rehabilitation Center

in the Limpopo province (September 2015; seven lions) in the Republic of South Africa. The animals were immobilized for clinical examination, Global Positioning System (GPS) collaring, deworming, contraceptive implantation and genetic material collection.

The BAM solution (BAM; Wildlife Pharmaceuticals South Africa (Pty) Ltd., South Africa) was prepared by dissolving one vial containing 300 mg of butorphanol tartrate, 120 mg of azaperone tartrate and 120 mg of medetomidine hydrochloride in 10 mL sterile water for injection (Pharma-Q water for injection; Pharma-Q, South Africa). Each millilitre of the solution contained 30 mg of butorphanol, 12 mg of azaperone and 12 mg of medetomidine. The individual doses for the combination were calculated based on commonly accepted recommendations for use of the above-mentioned active agents as well as the data acquired during previous immobilizations of lions conducted by the authors. The body weight of the animals was estimated based on visual parameters.

All the animals were immobilized between 6:00–13:00 and 15:00–17:00 hours in order to avoid high, midday environmental temperatures. The air temperature ranged from 4.0 °C to 33.4 °C. The elevation above mean sea level was 1399 m at Lechwe Lodge and about 520 m at the Moholoholo Rehabilitation Center.

A cartridge fired projector (Pneu-Dart Model 389; Wildlife Pharmaceuticals (Pty) Ltd.) was used to deliver the anaesthetic. Darts (Pneu-Dart Type 'C') with a volume of 1–3 mL and a length of 19–38 mm, and 13–16 gauge needles with wire barbs were used (Wildlife Pharmaceuticals (Pty) Ltd.). Remote darting was done in enclosures from inside a vehicle or on foot from distances ranging from 3 to 21 m. Distance was measured using Leupold RX-1000i rangefinder (Leupold & Stevens, OR, USA). The injections were administered into the femoral muscles.

For reversing the effect of the medetomidine in 13 cases, a formulation of 6.25 mg mL<sup>-1</sup> yohimbine hydrochloride at a dose rate of 0.2 mg kg<sup>-1</sup> body weight was used. In seven cases, atipamezole (Antisedan, 5 mg mL<sup>-1</sup>; Orion Pharma, Finland) at five times the medetomidine dose in milligrams was used. Naltrexone hydrochloride (Trexonil 50 mg mL<sup>-1</sup>; Wildlife Pharmaceuticals (Pty) Ltd.) was used to reverse butorphanol at one times (mg to mg) the actual butorphanol dose. All injections were administered intramuscularly (IM).

### Monitoring and manipulations of animals

Two stages of induction were timed: stage I—from the time of the darting until the first signs of sedation, including open mouth, ataxic gait and lowering of the head; stage II—from the injection time until sternal or lateral recumbency. Once the animals reached lateral recumbency, they were blindfolded and transported from the enclosure to a controlled environment, no further than 100 m from the enclosure, where monitoring could be performed. All animals were intubated using endotracheal tubes (Jorgensen Labs, CO, USA; 16–24 mm in diameter). Every 5 minutes, beginning at 15–20 minutes after darting, monitoring of physiological parameters [heart rate (HR), respiratory frequency ( $f_R$ ), oxygen saturation ( $SpO_2$ ), end-tidal carbon dioxide ( $Pe'CO_2$ ), noninvasive blood pressure and body temperature] was conducted using a veterinary monitor (Capnovet Deluxe Multiparameter Monitor; Eickemeyer, Germany). Auscultation using a stethoscope (3M Littmann Classic II S.E. Stethoscope; 3M, MN, USA) was performed every 5 minutes for the entire period of immobilization. The level of muscle relaxation was assessed based on the general muscle tone and position of the lower jaw using a 3-point scale. Level 1 indicates the absence of muscle tone, level 2 indicates a light tone and level 3 indicates a strongly marked tone. Capillary refill time and palpebral reflex were additionally registered.

Arterial blood samples were collected from the femoral or median caudal artery at 20, 30, 40 and 50 minutes after darting. The samples were immediately analysed using a portable analyser (i-STAT1 Portable Clinical Analyzer; Abaxis, CA, USA) and cartridges (i-STAT cartridges CG4+ & CHEM8+; Abaxis). Variables measured included pH, partial pressure of arterial oxygen ( $PaO_2$ ), partial pressure of carbon dioxide ( $PaCO_2$ ), lactate, haematocrit, sodium, potassium, chlorine, urea, creatinine, glucose and ionized calcium levels. Actual base excess, actual bicarbonate, arterial haemoglobin, oxygen saturation and haemoglobin were calculated from the measured values.

The animals were extubated 65–70 minutes after the beginning of immobilization provided a strongly marked palpebral reflex was observed. After extubation, all animals were weighed using a portable scale (Anyload OCSL Mini Crane Scale; Anyload Transducer Co., Ltd., BC, Canada) and transported back to the enclosure by vehicle. In the enclosure, the lions

were placed in the lateral position on the ground. Antagonists were then injected IM into the femoral muscle region. The following stages of recovery were recorded: time elapsed from injection until the first signs of recovery, including eye blinking time to head lifting, time to standing and time to fully coordinated movement (i.e., full recovery).

### Statistical analysis

For exploring the anaesthetic dosage effect on the lions' HR,  $f_R$ , systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP),  $SpO_2$ ,  $Pe'CO_2$ ,  $PaO_2$  and  $PaCO_2$ , and the area under the curve (AUC) was calculated using a trapezoid method for every measurement for the immobilization period (60 minutes). Linear regression models were used with the mean AUC as the response variable. The exact anaesthetic dosage used (calculated after weighing of immobilized lions) was divided into three levels (low: 0.52–0.56 mL 100 kg<sup>-1</sup>;  $n = 6$ , medium: 0.59–0.64 mL 100 kg<sup>-1</sup>;  $n = 8$ ; high: 0.66–0.83 mL 100 kg<sup>-1</sup>;  $n = 6$ ) as grouping variable and were included as an explanatory variable. Age was divided into two levels (subadults,  $n = 9$ ; adults,  $n = 11$ ) as the grouping variable and sex (males;  $n = 11$  and females;  $n = 9$ ), and their interaction with dose groups were added into every model. The model's assumptions were verified by scatter and normality plots of standardized residuals.

For comparing recovery time between different antidote groups (atipamezole;  $n = 7$  and yohimbine hydrochloride;  $n = 13$ ), a nonparametric Mann–Whitney test was used. For linear regression models and Mann–Whitney test, STATA 13.0 software (Stata Corporation, TX, USA) was used.

General linear mixed models (GLMMs) were used to explore the overall time trend in lactate, arterial blood pH and body temperature and differences in time trend between the dosage groups. Lions were included as random intercepts and polynomials of time (minutes), with interactions with the dosage group added as fixed effects in increasing order. The overall time trend differences between groups were tested using the  $F$  test. Isotropic spatial exponential covariance structure was used for modeling serial correlations of repeated measurements at the within-lion level in all models. Initially, sex and age group were included as fixed factors in all models. A backward elimination procedure was performed for the final models. The NLME package (Pinheiro J, Bates D, Debroy S,

Sarkar D: Linear and nonlinear mixed effect models; R package version 3.1-73, Austria; 2006) with statistical software R 3.2.2 (R-soft. R Development Core Team R: A language and environment for statistical computing; R Foundation for Statistical Computing, Austria; 2006) was used for fitting these GLMM models.

All fitted model assumptions were verified by scatter and normality plots of standardized residuals. A  $p$  value  $\leq 0.05$  was considered statistically significant. Data are reported as mean  $\pm$  standard deviation (range).

## Results

Data from 11 male lions weighing  $166 \pm 78$  (38–284) kg and from nine female animals weighing  $116 \pm 29$  (72–162) kg were used in this study. In all 20 animals, immobilization occurred after a single injection of BAM. There was no need for additional injections to achieve immobilization. The following dose rates were used: BAM volume dose rate range was  $0.005\text{--}0.008$  mL kg<sup>-1</sup> ( $0.006 \pm 0.001$  mL kg<sup>-1</sup> or  $0.6$  mL 100 kg<sup>-1</sup>). The total dose ranged from 0.3 to 1.6 mL. The actual doses were as follows: butorphanol,  $0.18 \pm 0.03$  g kg<sup>-1</sup>; azaperone,  $0.07 \pm 0.01$  mg kg<sup>-1</sup>; medetomidine,  $0.07 \pm 0.01$  mg kg<sup>-1</sup>. The first sign of induction occurred between 1 and 5 minutes after the injection ( $3 \pm 1$  minutes). The inductions were observed to be calm and smooth with no side effects. Vomiting was not observed in any of the lions. Five animals remained sleeping in sternal recumbency and never attained lateral recumbency but were immobilized; 15 lions went to lateral recumbency. The induction time ranged from 4 to 10 minutes ( $7 \pm 2$  minutes). There was no association between the variations in the BAM dose and the range of induction times recorded.

Immobilization was stable, and no sudden arousals were observed. Good muscle relaxation was evident in all cases. Low jaw muscle tone disappeared within 10–15 minutes after injection, except for one female lion whose low jaw muscle tone was still present 22 minutes after administration. Capillary refill times were less than 2 seconds, and mucous membrane colour was normal in all animals. Palpebral reflex disappeared at the 15th minute of the procedure and reappeared at the 45th–50th minute in the case of 12 animals, and at the 60th minute in the case of eight animals. In two animals, a weak palpebral reflex was registered during the entire period of immobilization. Four lions exhibited spontaneous limb twitches during the first 20 minutes of immobilization. None of the lions showed reaction to intubation, extubation or other painful procedures (e.g., blood collection). No apnoea was observed in any of the lions. One hour after the beginning of the procedure, during weighing, weak head and limb movements were observed ( $n = 14$ ). The duration of immobilization of one lion without additional doses was a little more than 1 hour.

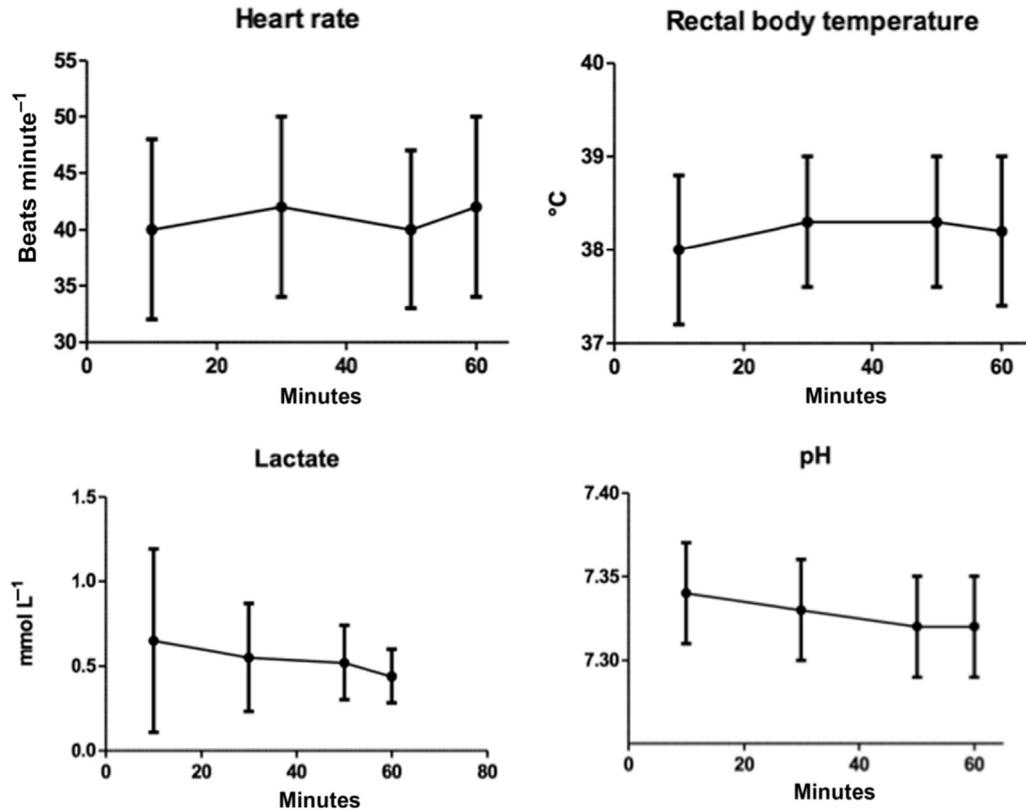
Table 1 presents the mean  $\pm$  standard deviation and range of the main monitoring variables, and Fig. 1 presents the measured physiological parameters during chemical restraint. Mean blood pH level ( $p < 0.001$ ) and lactate levels ( $p < 0.001$ ) steadily declined in all animals (Fig. 1). The administered dose (low:  $0.52\text{--}0.56$  mL 100 kg<sup>-1</sup>,  $n = 6$ ; medium:  $0.59\text{--}0.64$  mL 100 kg<sup>-1</sup>,  $n = 8$ ; high:  $0.66\text{--}0.83$  mL 100 kg<sup>-1</sup>,  $n = 6$ ) did not influence any of the physiological parameters tested.

There was a significant difference in recovery time after the administration of naltrexone and yohimbine [ $22 \pm 7$  (7–34) minutes;  $n = 13$ ] versus naltrexone and atipamezole [ $9 \pm 1$  (8–1) minutes;  $n = 7$ ] ( $p < 0.001$ ).

Variable		10–20 min <sup>1</sup>	20–30 min <sup>1</sup>	30–40 min <sup>1</sup>	Overall <sup>1</sup> (min–max)
PaO <sub>2</sub> <sup>3</sup>	mmHg	72 $\pm$ 3 (69–75)	76 $\pm$ 2 (74–78)	73 $\pm$ 3 (70–76)	72 $\pm$ 3 (68–78)
PaO <sub>2</sub> <sup>3</sup>	kPa	9.6 $\pm$ 0.4 (9.2–10.0)	10.1 $\pm$ 0.3 (9.9–10.4)	9.7 $\pm$ 0.4 (9.3–10.1)	9.6 $\pm$ 0.4 (9.1–10.4)
P <sub>E</sub> 'CO <sub>2</sub> <sup>4</sup>	mmHg	41 $\pm$ 4 (37–45)	41 $\pm$ 3 (38–44)	41 $\pm$ 3 (38–44)	41 $\pm$ 4 (32–49)
P <sub>E</sub> 'CO <sub>2</sub> <sup>4</sup>	kPa	5.5 $\pm$ 0.5 (4.9–6.0)	5.5 $\pm$ 0.4 (5.1–5.9)	5.5 $\pm$ 0.4 (5.1–5.9)	5.5 $\pm$ 0.5 (4.3–6.5)
PaCO <sub>2</sub> <sup>5</sup>	mmHg	45.0 $\pm$ 2.5 (42.5–47.5)	45.5 $\pm$ 1.9 (43.6–47.4)	46 $\pm$ 2.9 (43.1–48.9)	45 $\pm$ 2.5 (41–49)
PaCO <sub>2</sub> <sup>5</sup>	kPa	6.0 $\pm$ 0.3 (5.7–6.3)	6.1 $\pm$ 0.3 (5.8–6.3)	6.1 $\pm$ 0.4 (5.7–6.52)	6.0 $\pm$ 0.3 (5.5–6.5)

Average values are presented for the periods 10–20, 25–35, 40–50 and 55–60 minutes after darting and for the entire immobilization (overall). Results are presented as mean  $\pm$  standard deviation and (range).

PaCO<sub>2</sub>, partial pressure of arterial carbon dioxide (measured value, temperature corrected); PaO<sub>2</sub>, partial pressure of arterial oxygen (measured value, temperature corrected); P<sub>E</sub>'CO<sub>2</sub>, end-tidal carbon dioxide (measured by capnography); pH corrected to rectal temperature; SaO<sub>2</sub>, arterial haemoglobin saturation (calculated value, temperature corrected); SpO<sub>2</sub>, haemoglobin oxygen saturation (measured by pulse oximetry).



**Figure 1** The dynamics of heart rate, rectal body temperature, arterial blood pH and lactate (mean  $\pm$  standard deviation) during immobilization of African lions (10–60 minutes after darting) with a combination of butorphanol, azaperone, medetomidine (BAM).

## Discussion

The present study indicates that BAM is an efficient immobilization protocol for lions. The results show that induction time is similar to the BMM combination (Wenger et al. 2010), slightly longer than the tiletamine–zolazepam–medetomidine combination (Fahlman et al. 2005), but considerably shorter than the ketamine–xylazine combination (Stander & Morkel 1991). The therapeutic dose rate of BAM solution is wide and assures a high degree of reliability when using BAM under field conditions. Based on the present study, the recommended dose of BAM for healthy lions is 0.6 mL 100 kg<sup>-1</sup>. According to body weight, we recommend a total dose of 0.7–0.8 mL BAM for immobilization of an adult female or subadult male lion and a total dose of 1.0–1.2 mL for an adult male lion. The total volume of the drug is lower than the total volume of other combinations (Fahlman et al. 2005; Stander & Morkel 1991), which allows for the use of BAM with all types of remote delivery systems.

Only a few studies have reported on physiological parameters in detail in immobilized lions. The physiological parameters recorded during the present study were stable, and the cardiovascular parameters were within acceptable limits. A slight but stable bradycardia (defined as <50 beats minute<sup>-1</sup>) was observed in all lions immobilized with BAM (Table 1). The HR was slightly lower than those reported in other studies using tiletamine–zolazepam–medetomidine (Fahlman et al. 2005; Jacquier et al. 2006), BMM (Wenger et al. 2010) or ketamine and xylazine (Larsson et al. 2008). The HR was very similar to those in black bears immobilized with BAM (Wolf et al. 2008). The impact of dosage on HR and blood pressure does not seem to depend on the sex, body weight or the age of the animals. It can therefore be assumed that the bradycardia observed was because of the specific effect of medetomidine on peripheral  $\alpha_2$  adrenoreceptors resulting in an increase of systemic vascular resistant (Sinclair 2003). Rectal temperature initially increased in 14 lions, and this is similar to observations in other studies using alpha-2-

adrenoreceptor agonists (Fahlman et al. 2005; Jaquier et al. 2006; Wenger et al. 2010). Hyperthermia may have been caused by high ambient temperatures (19–38 °C) and interference with normal thermoregulatory mechanisms by alpha-2-adrenoreceptor agonists or opioids (Wenger et al. 2010). Arterial blood variables revealed the presence of mild metabolic acidosis during chemical restraint. Values for PaO<sub>2</sub>, arterial haemoglobin saturation (SaO<sub>2</sub>), PaCO<sub>2</sub>, pH and lactate remained within reference ranges reported for domestic cats (King 2004). The PaO<sub>2</sub> values were low and similar to values observed in lions immobilized with different drug combinations without additional oxygen supplementation (Fahlman et al. 2005; Wenger et al. 2010). The mean PaCO<sub>2</sub> in this study was 31.2 mmHg (4.16 kPa), which is within the normal range reported for domestic cats, indicating adequate ventilation (King 2004). It was also similar to PaCO<sub>2</sub> values observed in lions immobilized with a BMM combination (Wenger et al. 2010). The dose rate (low, medium or high) had no influence on heart rate, blood pressure or respiration parameters. This assures a high degree of reliability when practically applying the medication in field.

Using different reversal drugs clearly influences the recovery time and quality of recovery. The recovery time was significantly shorter when using naltrexone and atipamezole compared to when using naltrexone and yohimbine. Recovery with the naltrexone–atipamezole combination was smooth and occurred within 9 minutes. Animals showed signs of slight ataxia once standing during initial recovery. Recovery with the naltrexone–yohimbine combination was longer (22 ± 7 minutes) but still faster compared to the reported cases where a tiletamine–zolazepam–medetomidine combination was used in lions (mean time 33 minutes) (Fahlman et al. 2005). Thirteen lions reversed with yohimbine were severely ataxic, which may be explained by the incomplete reversal of the medetomidine by yohimbine.

In conclusion, the BAM combination at the doses used in this study proved to be a reliable immobilization protocol for lions. The advantages of BAM include a small drug volume for darting, calm and smooth induction, long duration of immobilization and ability to reverse the effects of immobilization drugs with naltrexone and atipamezole. Physiological parameters should be monitored throughout chemical restraint, and additional oxygen supplementation may be necessary.

## Authors' contributions

Conception and design of the study, or acquisition of data, or interpretation of data: AS, VA, JPR, TO, DV, LL, SP; drafting of article or revising it critically: AS, VA, JPR, TO, DV, LL, SP; final approval of manuscript: AS, VA, JPR, TO, DV, LL, SP.

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## Conflict of interest statement

Dr JP Raath is the owner of Wildlife Pharmaceuticals South Africa.

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