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Journal Articles

CHEMICAL IMMOBILISATION OF *HYLOBATES* SPP. USING TILETAMINE-ZOLAZEPAM AND ISOFLURANE OR KETAMINE

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SUMMARY

Hylobates spp. are native to Peninsular Malaysia and are listed as an endangered species on the International Union for Conservation of Nature (IUCN) Red List. Assessment of anaesthetic effects is paramount to improve immobilisation protocol in this species. This paper reports the anaesthetic effects and physiological parameters of 13 healthy gibbons induced with tiletamine-zolazepam (TZ) at 5 mg/kg, intramuscularly, and maintained with isoflurane (n = 8) or intravenous ketamine (n = 5) for health assessments. Tiletamine-zolazepam at a median dose of 5.19 mg/kg (interquartile range [IQR], 4.35-5.57 mg/kg) induced immobilisation, with gibbons showing no response to external stimuli at a median of 9 minutes (IQR, 5-14 minutes). Transient hypoxaemia occurred in five gibbons, which self-corrected as anaesthesia lightened or when oxygen was supplemented. Isoflurane maintenance produced more stable physiological parameters and deeper anaesthesia than intravenous ketamine. Hypotension with MAP below 50 mm Hg was detected in two gibbons under isoflurane. The recovery in the isoflurane group was smoother and shorter, with a median of 77 minutes (IQR, 48-88 minutes) compared to 125 minutes (IQR, 102-131 minutes) for ketamine. Two excitable gibbons experienced prolonged induction, requiring 24 and 53 minutes, respectively, to achieve recumbency. A nursing female with above-average body weight required 220 minutes to recover. No other adverse effects occurred. These findings indicate that TZ at 5 mg/kg IM is effective for immobilising captive gibbons. Anaesthesia may be extended with either isoflurane or ketamine. Supplemental oxygen and blood pressure support should be available.

Keywords: Hylobates spp., immobilisation, isoflurane, ketamine, tiletamine-zolazepam

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INTRODUCTION

Lar gibbons (*Hylobates lar*) and agile gibbons (*Hylobates agilis*) are native to Peninsular Malaysia, Thailand, and Sumatra, and are listed as endangered species on the International Union for Conservation of Nature (IUCN) Red List. Assessment of anaesthetic effects is essential to ensure safe immobilisation and animal welfare. Tiletamine-zolazepam (TZ) is widely used for immobilisation of primates due to its high potency and rapid onset. Tiletamine-zolazepam at a dose range of 2.2 to 4.4 mg/kg has been used for chemical restraint in lar gibbons (n = 8) (Eads, 1976, as cited in Ølberg, 2007). Use of medetomidine-zolazepam-tiletamine (n = 2) and ketamine-medetomidine (n = 38) has been reported in *Hylobates* spp. (Fahlman et al., 2006; Turner et al., 2018). Tiletamine-zolazepam, 5 mg/kg intravenously as induction, followed by maintenance with isoflurane, was used in a single case of fracture repair in a black gibbon (Yoon et al., 2009). However, these reports lack details of anaesthetic response times and physiological parameters. In particular, the comparative effects of isoflurane versus ketamine for anaesthesia maintenance following TZ induction have not been evaluated in gibbons. This paper aims to report the anaesthetic effects and physiological parameters of TZ induction, followed by maintenance with either isoflurane or ketamine in captive gibbons (*Hylobates* spp.), addressing gaps in induction and recovery responses as well as physiological monitoring.

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MATERIALS AND METHODS

Study design

This was an exploratory study using convenience sampling to evaluate the anaesthetic effects of TZ as an induction agent, followed by isoflurane or ketamine as maintenance agents in thirteen healthy gibbons at the Gibbon Rehabilitation Project (GReP) in Raub, Pahang, Malaysia, during health assessment procedures. Approval from the Universiti Putra Malaysia Institutional Animal Care and Use Committee (UPM/IACUC/AUP-T006/2024) and permission from Department of Wildlife and National Parks (PERHILITAN) were obtained for the health assessment. This study involved five female and six male lar gibbons, and two female agile gibbons, aged 4 to 13 years, with a median body weight of 5.20 kg (interquartile range [IQR], 4.36-5.42 kg). All gibbons were fasted overnight before the health assessments.

Induction

Tiletamine-zolazepam hydrochloride (Zoletil 100; Virbac, France), targeted at 5 mg/kg, was administered based on body weight estimated from visual appraisal and previous records. With distraction provided by the animal keeper, hand injection was administered intramuscularly (IM) into the biceps or brachial region. The times to the first signs of sedation, recumbency, and no response to external stimuli were recorded. Ketamine hydrochloride (Ilium Ketamil 100 mg/mL; Troy Laboratories, Australia), 1 mg/kg IM, was used as a supplementary anaesthetic when additional restraint was necessary. Following immobilisation, the gibbons were weighed, and the total anaesthetics administered were expressed as mg/kg based on actual body weight.

Maintenance and monitoring physiological parameters

A complete health examination was conducted after the gibbons were immobilised. Due to an unforeseen shortage of oxygen supply, five gibbons were maintained with intravenous (IV) ketamine, while eight gibbons were maintained with isoflurane (Isorane; Piramal Pharma Limited, India). Intubation was attempted only in the first gibbon. This individual exhibited continuous gagging reflexes, prompting extubation. Consequently, a face mask was used to deliver isoflurane for all the eight gibbons maintained under isoflurane. Physiological parameters, including pulse rate (PR), respiratory rate (RR), oxygen saturation (SpO_2), mean arterial pressure (MAP), and end-tidal carbon dioxide ($EtCO_2$), were recorded at 10-minute intervals using a veterinary monitor (RM800T Veterinary Monitor; RWD, USA). Pulse oximetry probe was placed on the ear pinna, whilst a non-invasive blood pressure cuff was placed on the brachium. End-tidal CO_2 was measured only on gibbons maintained with isoflurane, using side-stream sampling at the level of the face mask. Rectal temperature (RT) was measured using a digital thermometer (Omron; Kinsmedic, Malaysia).

Recovery

The time from the termination of isoflurane, and the time from the last top-up of ketamine to the time of first signs of recovery, the first attempt to sit or move, and being able to maintain steady movement were recorded. Head or limb movements and licking are considered the first signs of recovery. The time from the first sign of recovery to steady movement was compared between the isoflurane and the ketamine group.

Statistical analysis

Descriptive statistics were used for data analysis. The Shapiro-Wilk test was used to assess data normality. Time from first sign of recovery to steady movement between the ketamine and isoflurane groups was compared using the Mann-Whitney U test. The Friedman test was used to assess the time effects in the isoflurane group for PR, RR, SpO_2 and MAP. A *p*-value of less than 0.05 was considered significant.

RESULTS

Tiletamine-zolazepam (TZ) at a median dose of 5.19 mg/kg (interquartile range [IQR], 4.35-5.57 mg/kg) induced immobilisation, with gibbons showing no response to external stimuli at a median of 9 minutes (IQR, 5-14 minutes). Two gibbons received incomplete first TZ intramuscular injection doses and required further TZ top-up doses of 3.17 and 7.94 mg/kg; they achieved recumbency in 24 and 53 minutes, respectively. Three animals, including the two mentioned, required supplementary IM ketamine at doses of 3.17, 2.77 and 1.09 mg/kg, respectively. Time to achieve induction is shown in Table 1. Most gibbons exhibited the first sign of sedation as head lowering, whereas some displayed drowsiness.

The physiological parameters of the isoflurane group are shown in Table 2. Isoflurane settings and oxygen supply were administered in the range of 0.5-4 % and 0.5-1.25 L/min respectively; adjustments were made according to the desired anaesthetic depth for the health assessment procedures. There was no statistically significant change in PR, RR, SpO_2 and MAP under isoflurane maintenance, although PR and MAP showed a decreasing trend from 21 minutes onwards. SpO_2 levels below 94% were observed in three gibbons initially after induction, which increased to 97–100% following oxygen supplementation. Two gibbons exhibited hypotension, with MAP recorded at 42 mm Hg and 46 mm Hg, respectively.

The physiological parameters of the ketamine group are shown in Table 3. The PR, RR, SpO_2, and MAP of the ketamine group showed high variability. Four of the five animals required ketamine top-ups at a median dose of 1.11 mg/kg (IQR, 0.94-1.75 mg/kg, n = 4), IV at a median time of 19 minutes after TZ induction (IQR, 16-43 minutes, n = 4). Three animals required second ketamine top-ups at a median dose of 0.96 mg/kg (IQR, 0.92-1.21 mg/kg, n = 3) at a median time of 13 minutes (IQR, 4-21 minutes, n = 3) after first top-up. Two of the five gibbons in the ketamine group experienced SpO_2 levels below 94%, which self-corrected to above 95% as anaesthesia

Table 1. Body weights of gibbons (N = 13), dosage and time to effect of tiletamine-zolazepam (TZ)

Parameters	Body weight (kg)	Tiletamine-zolazepam (mg/kg)	T1 to: (min)		
			First sign of sedation	Recumbency	No response to external stimuli
Median	5.20	5.19	2	5	9
Q1-Q3	4.36-5.42	4.35-5.57	2-4	3-7	5-14
Range	3.24-5.85	2.40-6.27	1-11	2-53	3-62

N=number of samples; kg=kilogram; mg/kg=milligram per kilogram; T1=time of first TZ injection; min=minutes

Table 2. Physiological parameters of gibbons maintained with isoflurane

Parameter	Time after no response to external stimuli following induction							Time effects (Asymp. Sig.)
	0-10 min	11-20 min	21-30 min	31-40 min	41-50 min	51-60 min	61-70 min	
PR (beats/min)	107 (100-124) 99-131 n=7	126 (99-145) 97-168 n=7	119 (109-122) 96-152 n=8	113 (110-116) 107-120 n=7	108 (94-112) 89-113 n=6	111 (95-115) 91-116 n=4	92 (76-) 76-107 n=2	0.385
RR (breaths/min)	19 (16-31) 15-55 n=6	20 (19-27) 14-32 n=7	22 (19-35) 9-49 n=8	22 (20-30) 16-41 n=7	22 (16-34) 16-44 n=6	22 (20-37) 20-42 n=4	26 (19-) 19-32 n=2	0.976
SpO_2 (%)	94 (89-98) 85-100 n=5	100 (98-100) 96-100 n=7	99 (97-100) 92-100 n=8	100 (98-100) 95-100 n=7	100 (99-100) 97-100 n=6	100 (99-) 99-100 n=3	100 (99-) 99-100 n=2	0.083
MAP (mm Hg)	61 (52-) 52-66 n=3	59 (50-83) 42-128 n=6	57 (56-79) 54-95 n=6	56 (52-63) 46-74 n=7	60 (51-70) 51-74 n=6	56 (48-71) 47-74 n=4	64 (53-) 53-74 n=2	0.656
$EtCO_2$ (mm Hg)	30 (6-) 6-42 n=3	24 (8-) 8-26 n=3	27 (10-) 10-30 n=3	27 (21-32) 18-33 n=5	30 (23-33) 21-34 n=4	22 (17-31) 16-33 n=4	-	-
RT (°C)	38.4 (36.5-38.7) 35.9-38.8 n=4	36.5 (34.7-) 34.7-38.2 n=2	37.8 (37.4-) 37.4-38.1 n=2	37.4 (34.1-) 34.1-38.3 n=3	-	-	-	-

PR=pulse rate; RR=respiratory rate; SpO_2=oxygen saturation; MAP=mean arterial pressure; $EtCO_2$=end-tidal carbon dioxide; RT=rectal temperature; min=minutes; %=percentage; mm Hg=millimetres of mercury; °C=degrees Celsius; n=number of samples; Values are expressed as median (Q1-Q3) Min-Max

Table 3. Physiological parameters of gibbons maintained with intravenous ketamine

Parameter	Time after no response to external stimuli following induction		
	0-10 min	11-20 min	21-30 min
PR (beats/min)	117 (90-) 90-144 n=2	125 (85-152) 80-164 n=5	119 (79-160) 69-176 n=5
RR (breaths/min)	33 (30-) 30-36 n=2	28 (24-38) 20-44 n=5	28 (24-36) 20-40 n=5
SpO_2 (%)	96 (95-) 95-96 n=2	93 (89-98) 88-99 n=4	97 (95-) 95-100 n=3
MAP (mm Hg)	-	116 (82-) 82-150 n=2	-

PR=pulse rate; RR=respiratory rate; SpO_2=oxygen saturation; MAP=mean arterial pressure; min=minutes; %=percentage; mm Hg=millimetres of mercury; n=number of samples. Values are expressed as median (Q1-Q3) Min-Max

Table 4. Time from termination of isoflurane and last top-up of ketamine to various stages of recovery

Maintenance agent	n	TT to: (min)			Time from first sign of recovery to steady movement
		First sign of recovery	First attempt to sit or move	Steady movement	
Isoflurane	8	12 (2-26) 0-29	36 (19-54) 16-119	86 (59-104) 51-220	77 (48-88) 40-191
Ketamine	5	16 (10-51) 5-57	60 (31-80) 30-80	150 (122-167) 114-182	125 (102-131) 98-137

TT=time of isoflurane termination (isoflurane) or time of last ketamine administration (ketamine); n=number of samples; min=minutes. Values are expressed as median (Q1-Q3) Min-Max

lightened. No other adverse effects were observed. Throughout anaesthesia maintenance, gibbons maintained on isoflurane exhibited absent or weak medial palpebral reflexes, whereas those in the ketamine group showed strong palpebral reflexes. Nevertheless, the anaesthetic depths were adequate for biometric measurements, blood sampling, dental examination, chest radiography and abdominal ultrasonography in both groups. More gibbons in the isoflurane group were maintained beyond 30 minutes, whilst anaesthesia was kept short in the ketamine group to minimise top-ups and potential prolonged recovery.

The time from termination of isoflurane anaesthesia and last top-up of ketamine to the various stages of recovery are shown in Table 4. The isoflurane group generally had shorter recovery times, except for a female gibbon that required 220 minutes to achieve steady movement. Time from the first signs of recovery to achieve steady movement was significantly shorter in the isoflurane group compared to ketamine ($p = 0.028$).

DISCUSSION

Chemical immobilisation with TZ at a median dose of 5.19 mg/kg (IQR, 4.35-5.57 mg/kg), effectively induced safe immobilisation in gibbons, with a median time of 9 minutes to achieve no response to external stimuli. However, two gibbons, one male and one female, required

longer times likely due to their more aggressive and excitable temperaments. Excited or stressed animals typically experience prolonged induction times compared to calmer individuals (Caulkett & Arnemo, 2015). The variability in induction times highlights the challenges of accurately estimating dosages based on individual temperament.

Vital signs of gibbons maintained under isoflurane were more stable, reflecting a more controlled depth of anaesthesia. No significant time-related effects were observed in the isoflurane group during the 70-minute maintenance. This is consistent with previous work on neonatal rhesus macaques, whether maintained by isoflurane, ketamine or propofol in a controlled experimental setting (Martin et al., 2014). In contrast, gibbons under ketamine in the present study exhibited higher variability and fluctuations in the pulse rates and blood pressures, depending on the depth of anaesthesia and time of ketamine top-ups.

Two gibbons maintained under isoflurane recorded MAPs lower than 50 mm Hg, which resolved spontaneously without intervention. These episodes of hypotension may be attributed to the deep plane of anaesthesia, as well as the cardiovascular depressant effects of isoflurane. The relatively higher RR and MAP in the ketamine group may reflect the lighter anaesthetic plane, as gibbons maintained strong palpebral reflexes in this group. Gibbons maintained with ketamine recorded transient hypoxaemia, which resolved spontaneously as anaesthetic plane lightened. Therefore, supplemental oxygen should be readily available when using injectable anaesthetic protocols (Ølberg & Sinclair, 2014; Lee et al., 2010).

The significantly shorter recovery time observed with isoflurane compared to ketamine was consistent with previous studies demonstrating that isoflurane induces a faster and more responsive recovery than ketamine (Martin et al., 2014). Furthermore, recovery from isoflurane appeared smoother, with animals exhibiting fewer rocking movements than with ketamine. However, one female gibbon in the isoflurane group experienced the longest recovery time, taking 220 minutes. This gibbon was 11 months post-partum and still nursing her offspring. It weighed 5.85 kg but was induced based on a prior higher weight, resulting in a TZ dose of 5.98 mg/kg. The higher dose rate may have contributed to the longer recovery times.

Despite these promising results, the study has several limitations. The limited sample size and missing data precluded statistical analysis of some parameters. Furthermore, variations in the need for TZ and ketamine top-ups in some gibbons highlight the need to refine dosing protocols, taking into consideration the individual's temperament and body condition. Future studies with a larger sample size are required to address these gaps.

In conclusion, tiletamine-zolazepam is an effective and reliable agent for chemical immobilisation of gibbons. Isoflurane maintenance provides more stable physiological parameters and results in smoother and shorter recovery compared to ketamine. While isoflurane offers better welfare outcomes, equipment requirements may be a challenge in rugged field conditions. Hypoxaemia and hypotension may occur in susceptible individuals, thus, supplemental oxygen and blood pressure support should be available.

CONFLICT OF INTEREST

The authors declare no conflict of interest related to this study.

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