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Comparison of Butorphanol-Azaperone-Medetomidine and Nalbuphine-Medetomidine-Azaperone for Immobilization of White-Tailed Deer (*Odocoileus virginianus*)

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ABSTRACT: Butorphanol-azaperone-medetomidine (BAM) is commonly used for white-tailed deer (*Odocoileus virginianus*) immobilization in captive and free-ranging populations. It is a federally regulated controlled substance requiring stringent regulatory compliance, complicating field application. A prescription-only drug combination, nalbuphine-medetomidine-azaperone® (NalMed-A) provides a less-regulated alternative for use by wildlife professionals. Efficacy and safety of these drug combinations for immobilization of deer have not been compared in a controlled trial, and reports of dose-specific effects of NalMed-A on white-tailed deer physiology are lacking. Additionally, residual effects of these drugs on deer behavior, food consumption, and stress response have not been reported. In February through April 2021, we immobilized 30 captive female, adult white-tailed deer in three treatment groups (n=10 each). Hand-injected doses were 1.5 mL BAM intramuscularly (IM; 41.0 mg butorphanol, 13.6 mg azaperone, 16.4 mg medetomidine), 1.5 mL NalMed-A IM (60.0 mg nalbuphine, 15.0 mg medetomidine, 15.0 mg azaperone), and 2.0 mL NalMed-A IM (80.0 mg nalbuphine, 20.0 mg medetomidine, 20.0 mg azaperone). We compared quality of immobilizations and reversals and times to induction and reversal among treatments, collected biological samples to measure stress hormones and blood gases, and conducted observations to determine treatment-related variations in behaviors. When an effective dose was administered, both BAM and NalMed-A produced rapid and smooth immobilization and recovery after reversal. All treatments in combination with manual restraint caused some degree of hyperthermia, hypoxemia, hypercarbia, bradycardia, respiratory and metabolic acidosis, and elevated lactate and serum cortisol. At 60 d, all deer were still alive, with no apparent residual effects. Vital signs of deer exposed to manual restraint and these drug combinations should be monitored closely, with supportive therapy provided when needed. We suggest BAM and NalMed-A are safe for immobilizing deer in situations similar to our trials, although doses may perform differently in deer remotely injected without manual restraint.

Key words: Atipamezole, BAM, chemical immobilization, NalMed-A, naltrexone, stress.

INTRODUCTION

Capture and immobilization of white-tailed deer (*Odocoileus virginianus*) facilitates collection of important information including biological and telemetry-related data, which are useful for population management. Wildlife professionals also commonly use immobilizing drugs to restrain deer safely when facilitating public safety and animal welfare. The Animal Medicinal Drug Use Clarification Act of 1994 enables use of immobilizing drugs for wildlife capture with a valid veterinarian-client-patient relationship (Kreeger and Arnemo 2018). The compounded drug combination BAM (27.3 mg/mL butorphanol, 9.1 mg/mL azaperone, 10.9 mg/mL medetomidine; ZooPharm, Laramie, Wyoming, USA) is commonly used to immobilize captive and free-ranging deer. In the US, BAM is a Schedule IV controlled substance regulated by the U.S. Drug Enforcement Administration (DEA; U.S. Department of Justice 2020). The drug combination NalMed-A (40 mg/mL nalbuphine, 10 mg/mL medetomidine, 10 mg/mL

azaperone; ZooPharm) is a compounded prescription-only drug providing a less-regulated alternative to BAM in the United States (Wolfe et al. 2016b) and currently is used to capture a variety of wildlife (Wolfe et al. 2016a, 2020; Thomas et al. 2022).

Both BAM and NalMed-A were developed to facilitate capture of nondomesticated animals by remote delivery and to enable rapid recovery by drug antagonism (Lance and Wolfe 2010; Wolfe et al. 2016b). Capture, with or without chemical immobilization, may affect behavior, food intake, and stress levels of wildlife after release (Morellet et al. 2009; Brivio et al. 2015). However, postimmobilization physiological effects of BAM and NalMed-A on deer have not been investigated. Hand injection of captive wildlife provides experimental control and opportunities for extended observation not possible with darting of free-ranging animals; therefore, drug trials conducted at captive research facilities have provided wildlife professionals with important scientific knowledge (Kreeger et al. 1990; Miller et al. 2009; Wolfe et al. 2014).

Although the dose-specific effects of BAM and NalMed-A on deer physiology during immobilization have been reported independently (Mich et al. 2008, Miller et al. 2009, Siegal-Willott et al. 2009, Wolfe et al. 2016b), the efficacy of BAM and NalMed-A for immobilization of white-tailed deer has not been directly compared in published trials. Therefore, our objectives were to compare immobilization, reversal, and selected postanesthesia effects of BAM and NalMed-A in white-tailed deer.

MATERIALS AND METHODS

Research was conducted at the Whitehall Deer Research Facility at the Daniel B. Warnell School of Forestry and Natural Resources, University of Georgia, Athens, Georgia, USA (33°53′N, −83° 21′W, 194 m) during February–April 2021. Ambient temperature ranged from 8.9 to 24.0 C. Female deer used in this research were 1.5 y to an estimated >6.5 y old. Deer were provided with a pelletized ration (AntlerMax® Breeder 17-6, Purina Animal Nutrition, Arden Hill, Minnesota, USA), perennial peanut hay (*Arachis glabrata*), and water ad libitum. We housed deer by treatment group (n=10) in adjacent forested outdoor paddocks (0.4–0.8 ha) or individually in covered barn stalls (3 × 6 m). Deer were captive raised with temperaments subjectively ranging from calm to easily agitated, and were considered free of disease and injury based on year-round daily inspections. University of Georgia's Institutional Animal Care and Use Committee approved the study (Animal Use Proposal A2021 01-028-Y1-A2).

Immobilization treatments

We randomly assigned 10 females each to our treatment groups. Treatments based on existing manufacturer recommendations (ZooPharm) were BAM 1.5 mL (deer weight range 35–61 kg; 41.0 mg butorphanol, 13.6 mg azaperone, 16.4 mg medetomidine) and NalMed-A 1.5 mL (deer weight range 43–57 kg; 60.0 mg nalbuphine, 15.0 mg medetomidine, 15.0 mg azaperone). We also evaluated a 2.0-mL dose of NalMed-A (deer weight range 31–61 kg; 80.0 mg nalbuphine, 20.0 mg medetomidine, 20.0 mg azaperone). At 5 d before treatments, we moved deer from outside paddocks to individual barn stalls. To lower risk of aspiration of rumen content during immobilization, we fasted deer for ≥16 h before treatment (Lin and Walz 2014). At 0844–1815 hours on date of treatment (BAM 1.5 mL, 22 February; NalMed-A 1.5 mL, 10 March), we weighed deer to the nearest 0.5 kg (Tru-Test, Auckland, New Zealand), restrained them in a drop-floor chute, and hand-injected the treatment in a single intramuscular (IM) injection into their left hindquarter. We did not collect physiological data from deer in the chute, to minimize handling stress, and we standardized duration of physical restraint to approximately 1 min. Immediately after injection, we released deer into a 15 × 20–m observation pen, where we recorded time to the following effects: ataxia, head droop, sternal recumbency (sternal without rising), lateral recumbency (lateral without rising), head down (head touching ground) and safe to approach with no eye or ear reflexes observed (immobile and catatonic). Deer were approached to begin physical sampling once the safe-to-approach effect was reached. We used two independent observers, each with >20 y of deer capture experience, to rate immobilizations on a scale of 0–3 (with 3 being optimal) in the categories

of excitability, muscle rigidity, and overall quality of induction (18 was optimal and ≥12 was desirable; Storms et al. 2005).

At approach, we treated each deer's eyes with eye lubricant (Optixcare, CLC Medica, Waterdown, Ontario, Canada), covered them with a cloth blindfold, repositioned deer to ensure an open airway, and maintained them in a sternal position, supported by a researcher. We recorded rectal temperature (RT), heart rate (HR), and respiration rate (RR) after positioning deer at approach (T0), at 10 min postapproach (T1), and at 20 min postapproach (T2). We measured HR and hemoglobin oxygen saturation (SpO_2) with a pulse oximeter attached to the tongue (Rad-5 Masimo SET Handheld Pulse Oximeter, Irvine, California, USA), and validated accuracy of HR reading by auscultation. We measured RR by counting thoracic movements and RT with a digital thermometer (Neogen 8207 Digital Thermometer, Neogen Corporation, Lexington, Kentucky, USA). We monitored SpO_2 every 2 min and provided low flow (1.0 L/min, Fahlman et al. 2014) medical-grade oxygen through a vented mask (McCulloch Medical, Elmwood, Wisconsin, USA) when SpO_2 reached ≤70%. Once we began oxygen supplementation, we excluded from analyses subsequent SpO_2 and HR values. If RT reached a level consistent with hyperthermia necessitating intervention (41.1 C; Kreeger and Arnemo 2018), or ≥40 C and increasing, we protected deer from the sun's radiant heat by erecting a large umbrella and administered a cool-water enema (473–946 mL) via a 250-mL syringe and rubber catheter (Agri-Pro Enterprises, Iowa Falls, Iowa, USA; Nunez et al. 2020). We then excluded from analyses subsequent RT values.

We collected 10 mL of blood from the jugular vein via a 21-gauge × 25-mm needle and tube holder into additive-free blood collection tubes (Vacutainer, Becton Dickinson, New Jersey, USA) for serum cortisol analysis at T0, T1, and T2. To document significant disturbances in acid-base and blood gas values between treatment groups, arterial blood was collected from the auricular artery into heparinized syringes and analyzed immediately after collection with a point-of-care device (i-STAT, Abbott Point of Care Diagnostics, Princeton, New Jersey, USA). We analyzed pH, partial pressure carbon dioxide ($PaCO_2$), partial pressure oxygen (PaO_2), base excess (BE), bicarbonate (HCO_3), total carbon dioxide (TCO_2), percent blood oxygen (SaO_2), and lactate at T0, T1, and T2 using i-STAT CG4+ cartridges (Abbott Point of Care Diagnostics). When a blood sample could not be collected during T0, T1, or T2, we adjusted the sample size. For details see Supplementary Materials.

To antagonize the immobilizing drugs, we administered separate volume-based doses of 25 mg naltrexone (50 mg/mL; ZooPharm) and 75 mg atipamezole (25 mg/mL; ZooPharm) IM in the left hindquarter after collecting the T2 blood sample. For the 2.0-mL NalMed-A treatment, the dose of atipamezole was adjusted to 100 mg. We then monitored time to reversal stages: first sign of reversal (ear flick), head up, sternal recumbency, standing, and full recovery (no apparent sign of immobilization, e.g., ataxia). We used two independent observers, as previously described, to rate the quality of reversals on a scale from 0 to 3: 0 = extremely rough, lengthy, and potentially dangerous; 1 = rough or extended and unacceptable; 2 = relatively rapid and smooth, but could be improved; 3 = rapid, smooth, and optimal. Reversal ratings from each observer were summed for a possible range of 0–6 with a score of ≥4 considered desirable. After full recovery, we returned each deer to its barn stall.

Monitoring of deer behavior

We monitored deer behavior for 15 d before and after immobilization (i.e., 30 observations per deer). We recorded frequency of occurrence and duration of time spent standing, lying, moving, foraging, or being vigilant for each deer. We grouped behaviors into two categories: calm (calm movement, bedded relaxed, standing relaxed, foraging, grooming, and groomed) and alert (rapid movement, bedded alert, and standing alert; Supplementary Material Table S1). The first and last 10 d of the 30-d observation period, we monitored deer in outdoor paddocks where they were separated by treatment group. We opportunistically monitored the behavior of each deer for 10 min each day from an elevated observation tower near the center of the paddock. We waited 15 min after our arrival to begin recording behaviors, allowing time for deer to acclimate to our presence. For the 5 d immediately prior to and after treatment (days 11–20), we monitored deer behavior in individual barn stalls. We collected video recordings from a camera (Panasonic 25x

i.zoom, Panasonic Corporation, Kadoma, Osaka, Japan) mounted in the barn hallway adjacent to the stalls. After positioning the camera, we exited the hallway for 15 min, during which the camera recorded video. To minimize potential effects of our presence on behavior-related data, we used only the last 10 min of each video recording. After all deer in a treatment group had been videoed, we reviewed all recordings and classified each deer's behaviors.

Monitoring of fecal cortisol

To monitor individual and treatment-group fecal cortisol levels, we collected fresh fecal samples daily for 15 d before and after immobilization. We collected 10 random fecal samples (5–10 pellets for each sample from unique fecal piles) each day from each treatment group in paddocks for the first and last 10 d. To determine individual fecal cortisol levels, we collected fecal samples daily from deer in barn stalls at 4 d before treatment, on day of treatment, and 5 d posttreatment. We froze fecal samples at −20 C until subsequent processing and analysis. We dried samples for ≥24 h in an oven at 50 C, ground pellets using a mortar and pestle, and returned them to −20 C until subsequent analysis. We used cortisol ELISA kits (DetectX Cortisol ELISA Kits, Arbor Assays, Ann Arbor, Michigan, USA) according to manufacturer's guidelines for extraction of fecal cortisol metabolites. We weighed 0.2–0.4 g of ground fecal material and added 1 mL of 200-proof absolute ethanol (Fisher Scientific, Hampton, New Hampshire, USA) for every 0.1 g fecal material for extraction of cortisol. We shook the ethanol mixture for 30 min at room temperature on a rocking shaker, and pipetted the supernatant into 2-mL microcentrifuge tubes. The supernatant was either assayed directly or stored at −20 C for ≤30 d. We ran nine dilutions from 1:20–1:100 for a pooled fecal extract sample and reran any sample with a coefficient of variation (CV) >20%.

Monitoring of food consumption

We weighed each day's feed to the nearest 0.1 kg with a digital scale (Optima Scale Manufacturing Inc., Rancho Cucamonga, California, USA) daily for 15 d before and after immobilization. We calculated daily feed consumption by deer in outside paddocks and barn stalls by subtracting residual feed weight from the weight of feed provided the previous day. We calculated average individual consumption by dividing the weight of feed consumed by the number of deer in the group. While deer were in individual barn stalls, we were able to record specific feed consumption for each deer, but consumption totals were summed for group analysis.

Statistical analysis

We analyzed data using R 4.1.0 (R Core Team 2021). We used a one-way ANOVA with a post hoc Tukey-Kramer test to examine differences in time to effects, quality of induction and reversal, RT, HR, RR, serum cortisol, blood gases, and food consumption. Although we continued to record blood gas data after supplemental oxygen, we removed postsupplementation data from analysis. For behavioral observations, we analyzed frequency of calm and alert behaviors using a hypothesis-based linear mixed effects model with treatment and day as fixed effects and deer as a random effect. Significance for all data was set at $P<0.05$.

RESULTS

We included 10 deer in the BAM 1.5-mL treatment group. We used nine deer for the NalMed-A 1.5-mL treatment (one deer was excluded because she was given an incorrect dose), and nine deer for the NalMed-A 2.0-mL treatment (one deer was excluded because she experienced an injury during handling). All BAM 1.5-mL– and NalMed-A 2.0-mL–treated deer and eight of nine (89%) NalMed-A 1.5-mL–treated deer became immobile and catatonic 7–38 min after induction. However, a 51.4-kg deer injected with NalMed-A 1.5 mL went from lateral recumbency to standing at 31.0 min after injection when we attempted to blindfold her. At 59.5 min, she returned to sternal recumbency, but was too reactive to external stimuli to safely handle. Therefore, we administered antagonists, moved her to a barn stall until she fully recovered, and removed her from further data collection (i.e., adjusted $n=8$).

For all induction stages, time to effect was similar ($P>0.05$) among treatments (Table 1). Achievement of anesthesia was rapid and smooth with minimal excitement and muscle

TABLE 1. Time to effect (minutes; mean±SE) and quality rating of immobilization and subsequent reversal for white-tailed deer (*Odocoileus virginianus*) manually restrained in a drop-floor chute and hand injected intramuscularly with 41.0 mg butorphanol, 13.6 mg azaperone, 16.4 mg medetomidine (1.5 mL BAM, ZooPharm, Laramie, Wyoming, USA; n=10; 60.0 mg nalbuphine, 15.0 mg medetomidine, 15.0 mg azaperone; 1.5 mL NalMedA, ZooPharm; n=8), or 80.0 mg nalbuphine, 20.0 mg medetomidine, 20.0 mg azaperone (2 mL NalMedA; n=9) at the Whitehall Deer Research Facility, Athens, Georgia, USA, during February–March 2021.

Variable	BAM 1.5 mL[a] $\overline{X}$;±SE(range, n)	NalMed-A 1.5 mL[a] $\overline{X}$;±SE(range, n)	NalMed-A 2.0 mL[b] $\overline{X}$;SE(range, n)	P value
Immobilization[c]				
First effect	2.4±0.2 (1.5–3.7, 10)	2.6±0.2 (2.0–4.0, 8)	2.7±0.4 (1.8–5.0, 9)	0.83
Head droop	4.1±0.6 (2.9–9.6, 10)	4.0±0.3 (3.4–5.6, 8)	3.9±0.5 (2.5–6.0, 8)	0.09
Sternal recumbency	6.3±1.2 (3.3–15.7, 10)	6.5±1.5 (3.0–15.5, 8)	5.0±0.6 (3.0–8.0, 9)	0.17
Lateral recumbency	6.3±1.2 (3.3–17.7, 10)	7.0±1.4 (3.8–15.5, 8)	5.5±0.6 (3.0–8.0, 9)	0.10
Head down	8.5±2.1 (3.3–24.5, 10)	7.8±1.4 (3.8–15.5, 8)	5.8±0.6 (3.7–8.0, 9)	0.93
Safe to approach	14.7±2.6 (6.5–22.4, 10)	20.3±1.6 (14.5–23.3, 8)	20.4±2.6 (12.3–37.9, 9)	0.73
Quality rating[d]	13.4±1.3 (8–18, 10)	13.8±1.3 (9–18, 8)	12.8±0.9 (8–18, 9)	0.81
Reversal[e]				
First effect	3.6±0.5 (5.9–12.9, 9)	5.9±1.4 (2.3–12.9, 7)	4.9±0.5 (2.8–7.5, 9)	0.92
Head up	5.1±0.6 (2.3–7.0, 9)	7.8±1.8 (2.8–16.5, 8)	7.5±1.8 (4.0–13.4, 9)	0.65
Sternal recumbency	5.8±0.6 (2.3–7.6, 8)	8.6±1.9 (3.2–16.8, 8)	8.1±0.9 (5.0–13.7, 9)	0.77
Standing	6.9±0.5 (4.8–9.2, 9)	9.7±1.8 (3.4–16.8, 8)	9.1±0.8 (6.3–13.7, 9)	0.38
Full recovery	7.3±0.5 (5.0–9.4, 9)	11.0±1.9 (4.3–18.9, 8)	9.8±0.8 (6.5–10.8, 9)	0.34
Quality rating[f]	5.8±0.2 (4–6, 9)	5.1±0.4 (3–6, 8)	4.7±0.7 (0–6, 9)	0.35

[a] Antagonized with 75 mg atipamezole IM (25 mg/mL, ZooPharm) and 25 mg naltrexone IM (50 mg/mL, ZooPharm).
[b] Antagonized with 100 mg of atipamezole IM (25 mg/mL, ZooPharm) and 25 mg naltrexone IM (50 mg/mL, ZooPharm).
[c] Induction stages = time to ataxia, head droop, sternal recumbency (sternal without rising), lateral recumbency (lateral without rising), head down (head touching ground), and safe to approach (immobile and catatonic).
[d] Immobilization quality rating (18 was optimal and ≥12 was desirable; Storms et al. 2005) was determined by two independent reviewers.
[e] Reversal stages = first sign of reversal (e.g., ear flick), head up, sternal recumbency, standing, and full recovery (i.e., no sign of immobilization).
[f] Reversal quality ratings were evaluated on a scale from 0 to 3: 0 = extremely rough, lengthy, and potentially dangerous; 1 = rough or extended and unacceptable; 2 = relatively rapid and smooth, but could be improved; 3 = rapid, smooth, and optimal. A quality rating of 6 was optimal and ≥4 was desirable.

rigidity. Quality of immobilizations and reversals was similar (P>0.05) among treatments (Table 1).

Serum cortisol dilutions had equal concentrations (CV=7.7%) and were considered parallel to the standard curve. Across four plates, the intra-assay CV was 3.9% and inter-assay CV was 1.6%. Within treatments, serum cortisol trended downward over time and was lower at T2 than T0 within all three treatment groups (Table 2). Mean, standard error, and range for RT, RR, HR, and selected blood gas values (i.e., pH, lactate, $PaCO_2$, TCO2, PaO_2, SO_2, HCO_3, BE) at T0, T1, and T2 for each treatment group are presented in Table 2. Overall, there were no statistically significant differences (P>0.05) in the mean for each value at T0, T1, or T2 between the three treatment groups. However, some minor variation occurred within treatment groups, and other physiologically relevant findings are presented in the following.

Mean RT was similar at T0, T1, and T2 within each of the three treatment groups but RT were consistently elevated (>38.5 C) regardless of treatment group or time point (Table 2) (Nunez et al. 2020). In seven deer, RT increased above 41 C (hyperthermia, necessitating intervention, including two deer in the NalMed-A 2.0-mL treatment, two in the NalMed-A 1.5-mL treatment, and three in the BAM 1.5-mL treatment. In the NalMed-A 2.0-mL group, one

TABLE 2. Rectal temperature (RT; C), heart rate (HR), respiration rate (RR), pH, partial carbon dioxide ($PaCO_2$), partial oxygen (PaO_2), base excess (BE), bicarbonate (HCO_3), total carbon dioxide (TCO_2), percent blood oxygen (SpO_2), lactate, and serum cortisol (SC) measurements taken as soon as possible after time of safe approach (T0), 10 min after approach (T1), and 20 min after approach (T2) for white-tailed deer (*Odocoileus virginianus*) manually restrained in a drop-floor chute and hand injected intramuscularly with 41.0 mg butorphanol, 13.6 mg azaperone, 16.4 mg medetomidine (1.5 mL BAM, ZooPharm, Laramie, Wyoming, USA; n=10); 60.0 mg nalbuphine, 15.0 mg medetomidine, 15.0 mg azaperone (1.5 mL NalMedA, ZooPharm; n=8), or 80.0 mg nalbuphine, 20.0 mg medetomidine, 20.0 mg azaperone (2 mL NalMedA; n=9) at the Whitehall Deer Research Facility, Athens, Georgia, USA, during February–March 2021.

Variable[a]	BAM 1.5 mL $\overline{X}$;±SE(range, n)	NalMed-A 1.5 mL $\overline{X}$;±SE(range, n)	NalMed-A 2.0 mL $\overline{X}$;±SE(range, n)	P value
RT T0	40.4±0.6 (38.6–42.0, 10)	40.6±0.3 (39.9–41.3, 8)	40.3±0.3 (39.6–41.3, 9)	0.73
RT T1	39.9±0.5 (38.8–40.9, 8)	40.3±0.3 (39.7–41.0, 7)	40.0±0.3 (39.3–40.9, 8)	0.52
RT T2	39.7±0.3 (37.4–40.8, 7)	40.2±0.2 (39.8–40.6, 7)	39.8±0.5 (38.4–40.6, 8)	0.46
RR T0	21.2±2.5 (12–42, 10)	19.4±1.8 (12–24, 7)	16.9±2.1 (8–32, 9)	0.38
RR T1	21.6±3.0 (12–36, 10)	16.5±1.9 (12–24, 8)	17.8±2.4 (12–32, 9)	0.35
RR T2	20.4±2.5 (12–32, 9)	15.5±1.4 (12–20, 8)	16.8±2.5 (8–28, 8)	0.24
HR T0	59.6±5.8 (37–100, 10)	52.0±4.5 (36–69, 8)	65.9±5.7 (39–85, 9)	0.24
HR T1	56.3±7.2 (35–115, 10)	44.4±2.1 (33–52, 8)	49.9±3.0 (38–70, 9)	0.27
HR T2	43.4±2.9 (32–56, 7)	41.1±2.1 (31–48, 7)	45.9±4.5 (38–76, 8)	0.63
Lactate T0 (mmol/L)	8.9±1.4 (3.5–18.0, 10)	7.0±0.6 (3.9–9.0, 8)	8.8±1.4 (2.2–15.0, 9)	0.54
Lactate T1 (mmol/L)	7.6±1.4 (2.2–12.9, 10)	4.8±0.5 (2.5–6.1, 6)	6.9±1.2 (1.5–13.3, 9)	0.24
Lactate T2 (mmol/L)	5.9±1.1 (1.4–12.8, 7)	3.6±0.4 (2.0–4.7, 6)	5.0±0.9 (1.0–10.3, 8)	0.22
pH T0	7.24±0.03 (7.09–7.39, 10)	7.30±0.01 (7.25–7.36, 8)	7.27±0.03 (7.22–7.38, 9)	0.21
pH T1	7.28±0.02 (7.20–7.40, 10)	7.32±0.03 (7.28–7.44, 6)	7.30±0.02 (7.26–7.40, 9)	0.47
pH T2	7.29±0.02 (7.20–7.40, 7)	7.31±0.02 (7.30–7.38, 6)	7.32±0.02 (7.23–7.40, 8)	0.56
$PaCO_2$ T0 (mm Hg)	47.3±1.7 (40.6–53.6, 10)	46.1±1.8 (36.5–52.0, 8)	44.4±1.8 (34.3–50.4, 9)	0.50
$PaCO_2$ T1 (mm Hg)	45.8±1.5 (39.0–54.3, 10)	49.1±4.3 (32.0–49.8, 6)	45.4±2.1 (36.3–51.7, 9)	0.61
$PaCO_2$ T2 (mm Hg)	48.8±2.1 (38.7–54.0, 7)	51.1±4.2 (37.6–50.6, 6)	48.2±2.7 (37.8–51.9, 8)	0.79
TCO_2 T0 (mmol/L)	22±1.5 (14–28, 10)	24±1.2 (19–29, 8)	22±1.5 (16–28, 9)	0.51
TCO_2 T1 (mmol/L)	23±1.2 (18–29, 10)	26±1.0 (23–29, 6)	24±1.4 (18–28, 9)	0.22
TCO_2 T2 (mmol/L)	25±1.6 (16–31, 7)	27±1.3 (22–31, 6)	26±1.4 (20–31, 8)	0.65
BE T0 (mmol/L)	−7±1.8 (−17 to 2, 10)	−4±1.2 (−8 to 2, 8)	−7±1.9 (−15 to 2, 9)	0.40
BE T1 (mmol/L)	−5±1.5 (−10 to 0, 10)	-2±0.8 (−4 to 1, 6)	−4±1.7 (−12 to 3, 9)	0.22
BE T2 (mmol/L)	−3±1.7 (−13 to 5, 7)	-1±1.1 (−5 to 4, 6)	−1±1.6 (−9 to 5, 8)	0.60
PaO_2 T0 (mm Hg)	56±3.9 (43–77, 10)	64±10.9 (44–139, 8)	62±5.8 (45–105, 9)	0.70
PaO_2 T1 (mm Hg)	56±4.7 (41–73, 10)	84±17.5 (41–127, 6)	51±3.2 (39–72, 9)	0.07
PaO_2 T2 (mm Hg)	74±18.3 (42–87, 7)	74±17.5 (38–76, 6)	58±8.9 (40–68, 8)	0.63
SpO_2 T0 (%)	81±2.8 (68–91, 10)	85±2.7 (74–99, 8)	85±2.1 (75–97, 9)	0.37
SpO_2 T1 (%)	82±2.9 (70–93, 9)	88±3.4 (72–99, 6)	80±2.4 (68–93, 9)	0.17
SpO_2 T2 (%)	85±3.3 (70–95, 7)	86±3.7 (69–94, 6)	82±2.9 (71–92, 8)	0.60
HCO_3 T0 (mmol/L)	20.5±1.5 (12.6–26.7, 10)	22.6±1.1 (18.0–27.3, 8)	20.4±1.4 (15.2–26.8, 9)	0.47
HCO_3 T1 (mmol/L)	21.5±1.1 (17.2–27.4, 10)	24.5±0.9 (21.7–27.2, 6)	22.7±1.4 (16.5–29.2, 9)	0.23
HCO_3 T2 (mmol/L)	23.8±1.5 (15.1–29.5, 7)	25.6±1.2 (20.6–29.6, 6)	24.9±1.4 (18.9–29.6, 8)	0.66
SC T0 (µg/dL)	3.77±0.29 (2.18–5.32, 10)	2.73±0.19 (2.14–3.79, 8)	3.26±0.46 (0.72–4.97, 9)	0.12
SC T1 (µg/dL)	3.14±0.34 (1.92–4.30, 8)	2.15±0.17 (1.50–2.80, 8)	2.56±0.46 (0.63–5.32, 9)	0.12
SC T2 (µg/dL)	2.44±0.21 (1.50–3.36, 10)	1.46±0.14 (0.90–2.10, 8)	1.75±0.25 (0.48–3.02, 8)	0.12

[a] Rectal temperature was similar at T0, T1, and T2 for BAM 1.5 mL (P=0.91), NalMed-A 1.5 mL (P=0.73), and NalMed-A 2.0 mL (P=0.67). Heart rate was similar at T0, T1, and T2 for BAM 1.5 mL (P=0.13) and NalMed-A 1.5 mL (P=0.09), but declined from T0 to T2 for NalMed-A 2.0 mL (P=0.004). Respiration rate at T0, T1, and T2 was similar for BAM 1.5 mL (P=1.00), NalMed-A 1.5 mL (P=0.95), and NalMed-A 2.0 mL (P=0.99). Arterial blood gas measurements at T0, T1, T2 were similar within treatments (P>0.05), except for lactate for the NalMed-A 1.5-mL treatment, which was lower at T2 than T0 (P=0.003). Serum cortisol was lower at T2 than T0 for BAM 1.5 mL (P=0.006), NalMed-A 1.5 mL (P=0.0001), and NalMed-A 2.0 mL (P=0.04).

deer's RT decreased with shade and one deer received a cool-water enema after 2 min. In the NalMed-A 1.5-mL treatment, one deer's RT decreased with shade and one deer received an enema after 6 min. In the BAM 1.5-mL group, the three deer received an enema after initial RT reading, 2 min, and 14 min, respectively. Deer receiving an enema had subsequent RT data censored.

Mean RR was similar at T0, T1, and T2 within all three treatment groups ($P>0.05$), but five animals met the threshold for intervention based on degree of hypoxemia, $SpO_2 \leq 70\%$ calculated by iSTAT (Table 2). We provided supplemental oxygen to two BAM 1.5-mL–treated deer at 13.0 and 14.2 min after approach, two NalMed-A 1.5-mL–treated deer at 3.2 and 5.8 min after approach, and one NalMed-A 2.0-mL–treated-deer at 13.6 min after approach. At T2, SO_2 had increased in these deer: BAM 1.5 mL, 89% and 100%, NalMed-A 1.5 mL, 98% and 99%, Nalmed-A 2.0 mL, 98%.

Mean HR was similar within BAM 1.5-mL ($P>0.05$) and NalMed-A 1.5-mL ($P>0.05$) treatments, but for the NalMed-A 2.0-mL treatment, T1 and T2 were lower ($P=0.01$) than T0 (Table 2). Multiple deer exhibited bradycardia (HR<55 bpm; Haskins 2015) at T0 (BAM 1.5 mL, $n=4$; NalMed-A 1.5 mL, $n=5$; NalMed-A 2.0 mL, $n=2$), T1 (BAM 1.5 mL, $n=6$; NalMed-A, $n=8$; NalMed-A 2.0 mL, $n=8$), and T2 (BAM 1.5 mL, $n=6$; NalMed-A 1.5 mL, $n=7$; NalMed-A 2.0 mL, $n=7$).

Temperature affects blood gas analysis because the analyzers take measurements at normal body temperature of 37 C. All deer in the study experienced RT>37 C. However, these changes affected all treatment groups similarly; therefore no correction was made for actual body temperature. Within treatments, mean pH, $PaCO_2$, TCO_2, PaO_2, SO_2, BE, and HCO_3 did not significantly differ ($P>0.05$) at T0, T1, and T2 (Table 2). Mean lactate was higher ($P=0.003$) at T0 than T2 in the NalMed-A 1.5-mL treatment group (Table 2). Mean arterial pH, $PaCO_2$, and PaO_2 did not significantly differ at T0, T1, or T2 within or between treatment groups, but acidosis (pH<7.35; DelGiudice et al. 1994), hypercapnia ($PaCO_2$>45 mm Hg; Pon et al. 2016), and hypoxemia (PaO_2<60 mm Hg; Haskins 2015) were consistent features in all treatment groups.

There was no relationship between frequency of calm or alert deer behaviors and treatments (Table S2, Fig. S1). Fecal cortisol was outside the range of the linear portion of the standard curve with %B/B0 binding >80%. We could not use <1:20 dilution of extracts because of potential for assay interference. However, our replicates were within 20% CV, and all samples were <30 ng cortisol metabolites/g, suggesting no residual effects of our treatments.

Food consumption was similar ($P>0.05$) before and after treatments (Table S3), except that consumption increased ($P=0.0004$) for deer housed individually in barn stalls after the NalMed-A 1.5-mL treatment. Food consumption decreased when treatment groups were moved from group-housed outside paddocks to individual barn stalls ($P \leq 0.0001$).

DISCUSSION

Our results indicated that BAM (1.5 mL) and NalMed-A (1.5 or 2.0 mL) safely immobilized white-tailed deer without extended physiological or behavioral effects. Although one deer was not completely immobilized with 1.5 mL of NalMed-A, its level of immobilization was sufficient to allow approach for either a supplemental NalMed-A dose or to administer antagonists. Inclusion of this outlier in further data analysis was not possible, because the animal never reached predefined stages of immobilization and collection of physiological metrics was not possible. Giving a supplemental dose of immobilization drugs is not ideal, but commonly occurs because exact weights and stress levels of individuals are not known in field scenarios (DelGiudice et al. 2005) and because other factors (e.g., injection site) may lead to varying drug effects. Therefore, some individuals may require an increased dose (e.g., 2.0 mL) of NalMed-A to ensure immobilization.

Chemical immobilization interferes with an animal's ability to thermoregulate, because they

cannot respond physiologically (e.g., panting) or behaviorally (e.g., moving locations) to cool or warm themselves (Kreeger and Arnemo 2018). Normal RT in deer is 38.5 C (101.4 F), with an increase of 2 C being diagnostic of hyperthermia (Kreeger and Arnemo 2018) that might increase problems with acidemia, hypercarbia, and hypoxia (Chaney and Emmady 2023). In our study, some individuals in each treatment experienced hyperthermia and we intervened by administering a cool water enema. Exertion and stress associated with manual restraint before drug injection probably contributed to elevated RT, and possibly simulated responses similar to those caused by manual restraint techniques used to capture free-ranging deer. Hyperthermia is a predictable side effect when immobilizing drugs are combined with pursuit and manual restraint. Therefore, frequent monitoring of RT is essential, and intervention may be necessary and should be anticipated (Nunez et al. 2020). Our finding of bradycardia at T0, T1, and T2 in each of our treatments is not unexpected, because bradycardia and decreased cardiac output are common side effects of medetomidine immobilization of deer (Einwaller et al. 2020). Although HR>110 bpm is suggestive of tachycardia (Haskins 2015), only a BAM 1.5-mL–treated deer, which received supplemental oxygen, exceeded (T1=115 bpm) that threshold. Tachycardia may be attributed to increased stress and activity levels; this highlights the importance of minimizing human presence and other stimuli during capture, which may increase the excitability of deer prior to induction.

Immobilizing drugs contribute to respiratory depression in deer, and hypoxemia is of particular concern when combined with hyperthermia (Caulkett et al. 2000). Unfortunately, blood gas value reference ranges for adult, white-tailed deer at rest are not available as a baseline for comparison with our data. Based on our study design that included manual restraint and hand injection, our first time point (T0) probably represented some deviation from normal. Thus, blood gas analyses were performed to document significant deviations both within and between treatment groups. Because oxygenation varies with altitude, published reports relative to the low-oxygen threshold for hypoxemia also vary, for example PaO_2<86 mm Hg (Fahlman et al. 2014), PaO_2<80 mm Hg (Haskins 2015), PaO_2<74 mm Hg (Mich et al. 2008). Hypoxemia of anesthetized animals described as "profound," "severe," or "life-threatening" typically occurs at PaO_2<50–60 mm Hg (Caulkett et al. 2000; Read 2003; Haskins 2015). In white-tailed deer, PaO_2>60 mm Hg and SO_2>90% was considered adequate (Siegal-Willott et al. 2009; Muller et al. 2012). Multiple deer in each of our treatments had PaO_2 values suggestive of hypoxemia. The observed trends towards hypoxemia and arterial PCO_2>40–45 mm Hg with acidic blood pH were suggestive of respiratory acidosis (Burger and Schaller 2022), which may be associated with dose-dependent respiratory depression associated with immobilizing drugs (e.g., medetomidine; Kreeger and Arnemo 2018). Respiratory acidosis may be caused by hypoventilation resulting in reduced expiration of CO_2 (increase in $PaCO_2$) and a decrease in pH. The consistent hypoxemia (PaO_2<60 mmHg and SO_2<90%) that we observed was further evidence of hypoventilation. The HCO_3 concentration <24 mmol/L plus lactic acidosis suggested that metabolic acidosis also occurred, which has been observed in deer with other immobilizing drug combinations (Storms et al. 2006). The $PaCO_2$ remained high and PaO_2 low throughout all time points; therefore, we recommend using supplemental oxygen during chemical immobilization with these drug combinations.

Lactate concentration provides a prognostic test in mammals, including deer, regarding injury and illness (Allen and Holm 2008; Lorenzo et al. 2020). Each of our treatments commonly resulted in lactic acidemia (pH<7.35 and lactate>5 mmol/L; Boesch et al. 2011). Deer hand-injected with immobilizing drugs in a less stressful handling system at this facility had lower lactate concentrations before (4.1±0.6 mmol/L) and after (1.6±0.6 mmol/L) oxygen supplementation (Mitchell et al. 2021). Although each of the drug doses we

tested appear sufficient for immobilizing deer to facilitate safe handling, physical restraint and handling time should be minimized to lessen the potential for capture myopathy.

Serum cortisol is a sensitive indicator of traumatic stress in deer, increasing with duration of the event until an upper threshold is achieved (Gentsch et al. 2018). Method of capture affects serum cortisol levels (DelGiudice et al. 1990), with some remote delivery events using immobilizing drugs (e.g., remote dart delivery from a blind) being less stressful than various forms of manual restraint (DeNicola and Swihart 1997). DeNicola and Swihart (1997) defined baseline serum cortisol concentration in white-tailed deer at 4.1 ng/mL (0.41 μg/dL), and reported levels associated with darting and capture by drop net of 13.6 ng/mL (1.36 μg/dL) and 60.5 ng/mL (6.05 μg/dL), respectively. Serum cortisol concentration for white-tailed deer captured by cannon net and Clover trap were 3.88 μg/dL and 4.37 μg/dL, respectively (DelGiudice et al. 1990). Our results suggested that deer manually restrained in our drop-floor chute and immediately released into a confined space to facilitate observations experienced stress similar to that of free-ranging deer subjected to common capture methods. Although above baseline at T0, T1, and T2, serum cortisol concentrations in each of our treatments declined over time. This was expected, because serum cortisol declines gradually for 30–90 min after an acute stressor is removed, and azaperone and other drugs moderate cortisol response in deer when administered after manual restraint (DeNicola and Swihart 1997; Cattet et al. 2004, Mentaberre et al. 2010). Although we hoped to utilize fecal cortisol concentration as a potential metric for monitoring chronic stress in deer without physical capture as related to management (Vega et al. 2020), there is rapid decline in fecal cortisol of ruminants, which probably explains the undetectable levels as related to acute stress of our treatments (Palme et al. 2005). There is currently no appropriate noninvasive sample type to detect stress at the required time scale.

Either BAM or NalMed-A are appropriate choices for immobilization of white-tailed deer. The similarities of the physiological and immobilization effects of BAM and NalMed-A allow for use based on logistical factors rather than efficacy of each drug. Because NalMed-A is not DEA regulated (U.S. Department of Justice 2020), NalMed-A may be more readily accessible to personnel in the United States trained in capture and immobilization techniques. Nevertheless, a veterinarian is still required to prescribe NalMed-A and to ensure that safety procedures are in place. The option of a nonscheduled drug might enable broader research efforts and greater availability of personnel with immobilizing drugs to respond to wildlife emergencies. The compounding pharmacy currently suggests 1.5 mL of NalMed-A for adult white-tailed deer; we found that the effects of NalMed-A were similar across a wide range of weight-based doses. The valuable data our study has provided on NalMed-A in deer under controlled conditions needs to be complemented by additional studies in free-ranging deer (e.g., remote injection without restraint or fasting), including males in the experimental design to optimize its use in this species further, and application of these drug combinations via other capture methods (e.g., Clover trapping, netting, remote dart delivery). Finally, because all immobilizing drug combinations have negative side effects on deer physiology, it is important to monitor physiological processes and mitigate life-threatening complications.

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SUPPLEMENTARY MATERIAL

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