Article

Comparison of Intramuscular Ketamine–Medetomidine, Ketamine–Dexmedetomidine and Ketamine–Xylazine for Immobilization of Captive Rhesus Macaques (*Macaca mulatta*)

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Abstract: Anesthesia protocols in laboratory-held rhesus macaques (*Macaca mulatta*) are well described, but fewer reports exist in zoo, safari park or field environments. This study recorded and compared the level of sedation, heart rate (HR), respiratory rate (RR), and induction and recovery times of ketamine–medetomidine (KM), ketamine–dexmedetomidine (KD) and ketamine–xylazine (KX) protocols in ninety-five safari-park-managed rhesus macaques. In total, 31 animals received the KM protocol, which included 25 mg ketamine (6.08 ± 1.54 mg/kg) and 0.15 mg medetomidine (0.04 ± 0.01 mg/kg); 33 animals received the KD protocol, which included 25 mg ketamine (6.19 ± 2.42 mg/kg) and 0.08 mg dexmedetomidine (0.02 ± 0.01 mg/kg); and 31 animals received the KX protocol, which included 50 mg ketamine (12.64 ± 3.79 mg/kg) and 1.2 mg xylazine (0.30 ± 0.09 mg/kg). Anesthesia was reversed with atipamezole. The mean bodyweight of the study population was lower than expected, so actual doses were higher than intended; no adverse effects were reported. Induction and recovery times were longer for KX than KD or KM ($p < 0.05$) but did not differ significantly between KD and KM ($p > 0.05$). HR and RR did not differ between protocols ($p > 0.05$). Sedation score was negatively correlated with bodyweight, and mean sedation score was lower for KX than KM or KD. KD and KM provided more rapid and reliable sedation than KX at the doses described; however, alterations in the KX dose may improve reliability.

Keywords: macaque; immobilization; anesthesia; ketamine; α-2 agonist; atipamezole

1. Introduction

Wild rhesus macaques (*Macaca mulatta*) range from Afghanistan to the eastern extent of China, and south into Thailand [1], and are currently listed as Least Concern by the International Union for Conservation of Nature [2]. Anesthesia studies on zoo-managed and free-ranging Macaca spp. are reported [3,4], but most studies come from laboratory populations where macaques are commonly used in biomedical research [5–10]. Requirements for anesthesia in field settings are a rapid induction, good quality immobilization and a rapid and smooth recovery [11]. Rhesus macaques are commonly held in zoos and safari parks in large naturalistic troops, with interventions performed in multiple animals at a time; the desirable characteristics of chemical immobilization protocols in these environments are therefore more analogous to a field setting.

Anesthesia is usually required in primates to allow for safe handling for personnel during veterinary procedures, and to relieve stress, pain or discomfort for the animal [12]. Of particular zoonotic concern when handling macaques are simian retroviruses and B-virus (*Macacine alphaherpesvirus* 1) [13–15].

While alternative combinations have been described [16–21], dissociative anesthetic agents (usually ketamine) combined with an α-2 adrenoceptor agonist (α-2 agonist) or benzodiazepine are the most commonly utilized anesthetic protocols for primates [12,22–25]. Ketamine is a phencyclidine derivative that results in anesthesia characterized by a short induction time and significant analgesia, but marked muscle rigidity [9,26]. Compared with ketamine alone, the addition of medetomidine provides deeper and more reliable immobilization, improved muscle relaxation, and no extension of induction or recovery times [6,27]. Dexmedetomidine is the clinically active enantiomer of medetomidine [28,29]. Its use is less well documented in primates, but it is reported to provide rapid and smooth inductions, good muscle relaxation and few side effects [30–33]. The addition of xylazine to ketamine in rhesus macaques has been found to enhance analgesia and muscle relaxation; this combination has a wide safety margin, although sudden recoveries have been reported and xylazine has been shown to cause sharp reductions in rectal temperature [3,7,34].

The availability of α-2 agonists varies with geographical location and while in the author's experience (JMC) xylazine is relatively simple to obtain, availability of medetomidine and dexmedetomidine is variable in range countries. To the authors' knowledge, there have been no studies directly comparing the induction and recovery times, and sedative properties of three well-described α-2 agonist and ketamine protocols during a single immobilization event in a large troop of safari-park-managed rhesus macaques; this was the aim of the study. The hypothesis was that ketamine–medetomidine (KM) and ketamine–dexmedetomidine (KD) would provide a more rapid and reliable sedation than ketamine–xylazine (KX), but that all three protocols would provide safe and effective immobilization for minor procedures in macaques at the doses described.

2. Materials and Methods

2.1. Study Population

A troop comprising 102 rhesus macaques was immobilized at Longleat Safari Park, Warminster, BA12 7NW (UK), during a single day in January 2016 for routine health screening and disease surveillance. The animals were managed in a large drive-through exhibit incorporating a house that could be used to contain individuals if required; contact with the animals was otherwise minimal and they were not trained for voluntary participation in health care procedures. Procedures were performed as part of a routine preventative medicine program.

Individuals were fasted between 12 and 24 h, depending on order of anesthesia; water was not withheld. Animals were confined indoors in a chute system, from where they were sequentially moved forwards into a squeeze cage and physically restrained. Anesthetic agents were administered by hand injection, intramuscularly (IM) into the hindlimb by a single anesthetist (JMC). Restraint was then released, and the squeeze cage covered, allowing time for induction agents to take effect.

Anesthetic protocols were allocated using a repeating pattern of ketamine–medetomidine (KM), ketamine–dexmedetomidine (KD) and ketamine–xylazine (KX). The single anesthetist (JMC) was aware of which protocol had been administered to maximize the safety of the animals and associated personnel.

Total anesthetic dosages comprised 25 mg ketamine (Ketamidor, Chanelle Pharma UK, 483 Green Lanes, London, N13 4BS, UK; 100 mg/mL) with either 0.15 mg medetomidine (Domitor, Vetoquinol UK Ltd., Paulerspury, Towcester, NN12 7LS, UK; 1 mg/mL) or

0.08 mg dexmedetomidine (Dexdomitor, Vetoquinol UK Ltd.; 0.5 mg/mL); or 50 mg ketamine and 1.2 mg xylazine (Sedaxylan, Eurovet Animal Health BV, 5531 AE Bladel, The Netherlands; 20 mg/mL). Drug doses were based on an estimated average bodyweight of 5 kg. Calculated doses were expected to be approximately 5 mg/kg ketamine combined with either 0.03 mg/kg medetomidine or 0.016 mg/kg dexmedetomidine; or 10 mg/kg ketamine combined with 0.24 mg/kg xylazine.

Once injected, macaques were visually assessed, and when recumbent, a pole was used to test the depth of anesthesia and response to external stimuli. Once a macaque was deemed safe to handle based on a lack of response to external stimuli or purposeful movement, it was removed from the cage and placed on the examination table. If animals were deemed unsafe to handle after the initial dose, supplemental doses were administered while the animal remained in the squeeze cage; these consisted of half of the initial dose of both induction drugs. Induction time was defined as the duration between the administration of the induction agents to when an animal could be safely removed from the squeeze cage.

Degree of sedation was assessed immediately after the macaque was removed, and each animal was scored by the same anesthetist based on a simple descriptive scale ranging from 0 to 3 (Table 1). Heart rate (HR) and respiratory rate (RR) were obtained immediately after this, along with bodyweight (kg). HR was measured by auscultation of the chest over a 30 s period, and RR was taken visually, also over a 30 s period. Animals underwent clinical examination, microchipping if required, comparative intradermal palpebral tuberculin testing, and blood sampling for routine hematology, biochemistry and relevant serology/disease screening.

Table 1. Classification of sedation score for rhesus macaques (*Macaca mulatta*) under anesthesia with either ketamine–medetomidine, ketamine–dexmedetomidine or ketamine–xylazine protocols. A single anesthetist assessed all macaques and assigned the score.

Sedation Score	Criteria
0	No sedation; sitting up; normal response to external tactile/auditory stimuli, exhibiting spontaneous movements; spontaneously blinking.
1	Mild sedation; recumbent; some response to external tactile/auditory stimuli; occasional spontaneous movements; strong palpebral reflexes.
2	Moderate sedation; recumbent; no response to external tactile/auditory stimuli; no spontaneous movements; weak palpebral reflexes.
3	Heavy sedation/surgical plane of anesthesia; recumbent; no response to external tactile/auditory stimuli; absent palpebral reflexes.

Once the procedure was completed, animals were moved to a straw filled enclosure. Atipamezole (Atipam, Dechra Veterinary Products, Sansaw Business Park, Hadnall, Shrewsbury, Shropshire, SY4 4AS, UK; 5 mg/mL) was administered IM at the following doses: 0.75 mg in the KM group, 1 mg in the KD group and 0.25 mg in the KX group. Procedure time was defined as duration from squeeze cage removal to administration of atipamezole.

Animals were monitored visually for signs of recovery in the period following atipamezole administration and were considered fully recovered when they were standing, non-ataxic and fully responsive to external stimuli. Duration from administration of atipamezole to full recovery was recorded as the recovery time. Total immobilization time was defined as the total time elapsing between the administration of induction agents

and full recovery. Macaques were kept inside overnight and released into the exhibit the following day.

2.2. Statistical Methods

Statistical analyses were performed using RStudio® software (Version 9.1.494; RStudio Team, 2023, Boston, MA 02210, USA), and significance throughout the study was set at $p < 0.05$. Means, standard deviations (SDs), ranges and coefficients of variation (CV) were calculated for all continuous variables. Fisher's exact test with Freeman–Halton extension was used to determine if there was a significant difference between the sex ratios of the three protocol groups. Boxplots were created to visualize the distribution of induction and recovery times, and sedation score between protocols. Normal distribution of data within each protocol was examined using the Shapiro–Wilk test, histograms and Q-Q plots. Because bodyweight and RR were found to be normally distributed across all three protocols, a one-way ANOVA was performed to investigate significant differences in these variables between groups; induction, immobilization and recovery times, as well as HR, violated assumptions for parametric tests and so a Kruskal–Wallis test was used instead. Pairwise post hoc analyses were performed using Tukey HSD (parametric) or Dunn–Bonferroni (nonparametric) tests. As reliable immobilization and rapid inductions and recoveries are important considerations in the choice of anesthesia protocol, Levene's test for homogeneity of variance was used to test for significant differences in the variability of induction times, recovery times and sedation scores between protocols. Spearman's correlation coefficient was calculated to test for a correlation between weight and sedation score (in the whole population and within each protocol group), as well as between the total induction dose administered (on a mg/kg basis) and each of the other continuous variables, within each protocol group.

3. Results

One hundred and two rhesus macaques were immobilized. Criteria for inclusion in the statistical analysis comprised apparent normal health status (no health concerns significant enough to potentially impact the effect of immobilizing drugs) and administration of a full induction dose and any required supplementation, and a full antagonist dose. In total, 95 juvenile to adult macaques met the criteria (83 females, 12 males). Mean weight was 4.43 ± 1.15 kg ($n = 92$; range 1.67–7.66 kg, median 4.47 kg). There was no significant difference in mean weight or sex ratio between the three drug protocol groups ($p = 0.689$), although each group consisted of significantly more females than males.

Thirty-one macaques were immobilized with KM, 33 with KD and 31 with KX. In three cases ($n = 1$ from each protocol group), an additional induction dose was necessary for effective immobilization. This was administered within 5–9 min of the first injection and included in the calculation of average doses. Mean procedure time in all macaques was short, at 4.51 ± 1.44 min (range 1–11 min). Dose rates and differences between the protocols, along with descriptive statistics, can be found in Table 2 and Figure 1.

Table 2. Immobilization timings, physiologic values, sedation scores, weights and drug doses of rhesus macaques anesthetised with ketamine–medetomidine (KM), ketamine–dexmedetomidine (KD), and ketamine–xylazine (KX) protocols. Mean values, SDs, ranges and coefficients of variation (CV) are given. Differences between protocol groups are presented as the *p*-value for each pairwise comparison obtained from post hoc testing (Tukey for parametric variables and Dunn–Bonferroni for nonparametric variables). Significant *p*-values (<0.05) are in bold [a].

Variable [b]	KM (n = 31; M 5, F 26) Mean ± SD	CV	Min.–Max.	n	KD (n = 33; M 3, F 30) Mean ± SD	CV	Min.–Max.	n	KX (n = 31; M 4, F 27) Mean ± SD	CV	Min.–Max.	n	Tukey HSD or Dunn–Bonferroni p-Value KM/KD	KD/KX	KX/KM
Induction (min) [N]	4.50 ± 1.25	0.29	3–8	30	4.24 ± 1.73	0.41	2–12	33	5.48 ± 2.29	0.42	2–12	31	0.261	**0.022**	0.325
Recovery (min) [N]	29.03 ± 15.00	0.52	11–67	30	22.87 ± 12.34	0.54	7–58	31	39.16 ± 18.16	0.21	9–73	31	0.203	**<0.001**	**0.002**
Immobilization (min) [N]	37.87 ± 14.50	0.38	21–77	30	31.55 ± 12.39	0.39	18–69	31	49.13 ± 17.80	0.36	19–81	31	0.150	**<0.001**	**0.001**
Heart rate (bpm) [N]	101.66 ± 21.92	0.22	40–144	29	106.55 ± 15.23	0.14	84–144	33	114.86 ± 18.60	0.16	84–156	28	0.563	0.201	0.059
Respiratory rate (bpm) [P]	36.14 ± 11.54	0.32	16–60	29	38.06 ± 12.01	0.32	16–72	33	33.43 ± 8.09	0.24	20–48	28	0.764	0.222	0.611
Sedation score [N]	2.13 ± 0.81	0.38	0–3	31	2.15 ± 0.57	0.27	1–3	33	1.81 ± 0.75	0.41	1–3	31	0.965	0.056	0.055
Weight (kg) [P]	4.34 ± 0.97	0.22	2.78–6.14	29	4.52 ± 1.22	0.27	1.67–6.44	33	4.40 ± 1.24	0.28	2.18–7.66	30	0.818	0.904	0.983
Ketamine (mg/kg) [N]	6.08 ± 1.54	0.25	4.07–8.99	29	6.19 ± 2.42	0.39	3.88–14.97	33	12.64 ± 3.79	0.30	6.53–22.94	30	0.764	**<0.001**	**<0.001**
Medetomidine (mg/kg)	0.04 ± 0.01	0.25	0.02–0.05	29	-	-	-	-	-	-	-	-	-	-	-
Dexmedetomidine (mg/kg)	-	-	-	-	0.02 ± 0.01	0.5	0.01–0.05	33	-	-	-	-	-	-	-
Xylazine (mg/kg)	-	-	-	-	-	-	-	-	0.30 ± 0.09	0.3	0.16–0.55	30	-	-	-
Atipamezole (mg/kg) [N]	0.18 ± 0.05	0.28	0.12–0.27	29	0.25 ± 0.10	0.40	0.16–0.60	33	0.06 ± 0.02	0.33	0.03–0.12	30	0.056	**<0.001**	**<0.001**

[a] Induction: time between administration of induction agents to when animal could be safely handled and removed from the squeeze cage; recovery: time between administration of reversal agent and animal being deemed fit for release; immobilization: total time elapsing between administration of induction agents and animal being deemed fit for release; bpm: beats/min (heart rate) or breaths/min (respiratory rate); sedation score: subjective evaluation of immobilization efficacy using a scale of 0 (none) to 3 (full effect); kg, kilograms; mg/kg, milligrams per kilogram of body weight. [b] Superscripts after each variable indicate either parametric (P) or nonparametric (N) distribution. Comparisons between protocol groups performed using one-way ANOVA for parametric variables and Kruskal–Wallis for nonparametric variables, followed by Tukey or Dunn–Bonferroni post hoc tests, respectively.
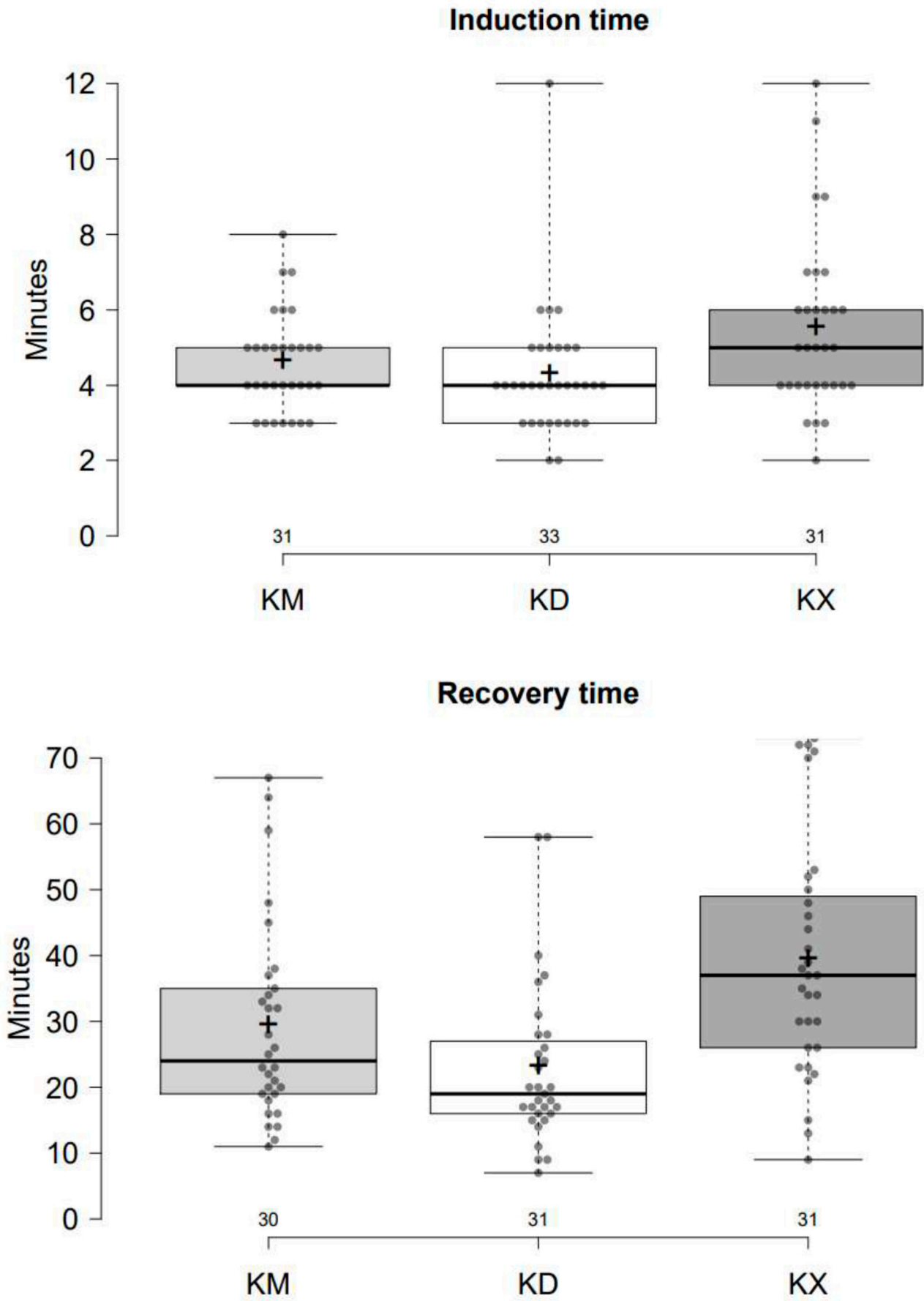
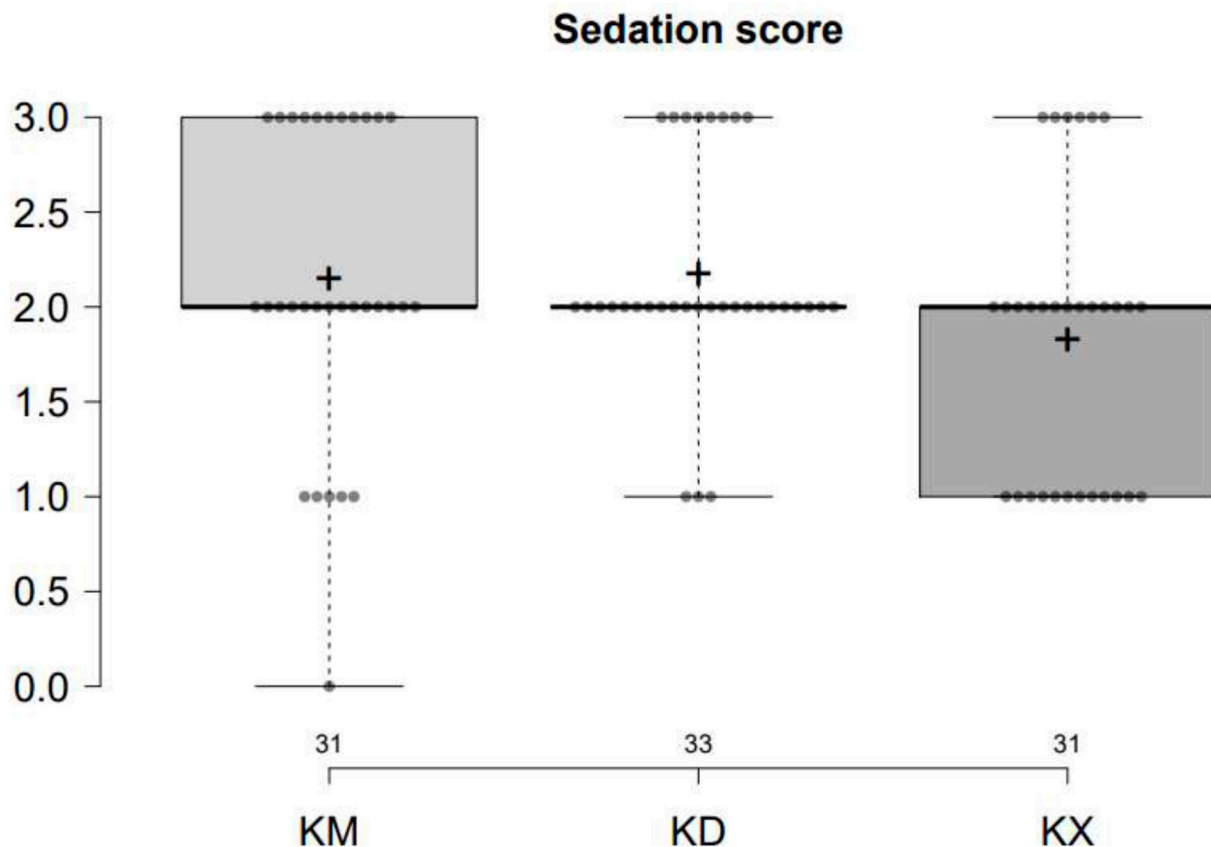**Figure 1.** *Cont.*

Sedation score

Figure 1. Box plots of induction and recovery time, and sedation score for rhesus macaques anaesthetized with ketamine–medetomidine (KM), ketamine–dexmedetomidine (KD), and ketamine–xylazine (KX) protocols. Times are given in minutes. Sedation score was determined by a single anesthetist using a subjective scale of 0 (no immobilization effect) to 3 (full immobilization). *n* in groups is given above protocol abbreviation. Box limits indicate the range of the central 50% of values; a cross marks the mean value. Lines extending from each box indicate the range of the remaining values and dots represent all datapoints.

In all protocols, the results of the Spearman correlation indicated a non-significant, small, negative relationship between total dose and induction time (KM, r(27) = −0.236, $p = 0.222$; KD, r(31) = −0.151, $p = 0.401$; KX, r(28) = −0.11, $p = 0.562$) but a significant, large, positive relationship between total dose and recovery time (KM, r(27) = 0.63, $p < 0.001$; KD, r(29) = 0.501, $p = 0.004$; KX, r(28) = 0.566, $p = 0.001$).

The means and ranges of HR and RR measured immediately after completed induction did not differ significantly between protocol groups (all $p > 0.05$). Macaques immobilized with KX had both the highest mean HR and the lowest mean RR. There was a significant, moderate, positive relationship between total induction dose and RR in both KM (r(27) = 0.455, $p = 0.016$) and KX (r(26) = 0.4, $p = 0.035$), while this relationship was insignificant in macaques immobilized with KD (r(31) = 0.253, $p = 0.155$). HR was not significantly correlated with dose in any protocol.

Mean sedation score for macaques immobilized with KM and KD were similar (2.13 ± 0.81 and 2.15 ± 0.57, respectively), and slightly higher than those immobilized with KX (1.81 ± 0.75). Except for a single macaque that failed to become effectively immobilized in the KM group (sedation score 0), scores within each protocol ranged between 1 and 3. Within the whole study population, there was a significant, moderate, negative relationship between body weight and sedation score (r(90) = −0.462, $p < 0.001$). This negative correlation was observed within each protocol group, and was the greatest for KD (KD, r(31) = 0.588, $p < 0.001$; KM, r(27) = 0.389, $p = 0.037$; KX, r(28) = 0.479, $p = 0.007$). As expected,

within all protocols, there was a significant, moderate, positive relationship between total dose and sedation score, which was also greatest for the KD protocol (KD, $r(31) = 0.5$, $p = 0.003$; KM, $r(27) = 0.415$, $p = 0.025$; KX, $r(28) = 0.375$, $p = 0.041$). Levene's test indicated no significant difference in the variance of sedation scores ($F = 2.48$, $p = 0.09$), induction times ($F = 2.27$, $p = 0.109$) or recovery times ($F = 2.27$, $p = 0.109$) between protocols.

4. Discussion

The aim of this study was to directly compare the sedative properties and basic physiological effects of three commonly used ketamine and α-2 agonists protocols during a single immobilization event in a large troop of safari-park-managed rhesus macaques. The maximum combined drug volume was 0.56 mL (KX), facilitating injection by hand syringe; this volume would also fit comfortably inside a dart. The inherent stress of this type of procedure in a sizeable troop of primates is largely unavoidable, and therefore rapid inductions and recoveries are paramount, particularly where early post-immobilization reintegration is required. This study allowed for direct comparison of timings and sedation scores between three well-described anesthetic combinations where animal weights were not known prior to induction, but where post anesthesia monitoring was possible, reflecting a common scenario with management of a large troop of captive primates.

The study population exhibited low mean bodyweight when compared to that reported in wild populations of adult rhesus macaques [35,36], largely attributable to inclusion of immature animals. The heaviest animal was only 7.66 kg, falling short of the upper weight of 10.9 kg reported in wild macaques of both sexes [35]. As a result of the unexpectedly low mean bodyweight, the average actual KM, KD and KX doses administered were higher than the targeted dose by 21.7%, 23.8% and 26.3% respectively. Of the 12 males included, only one was considered adult based on physical characteristics and bodyweight (6.78 kg); in contrast, 56/83 of females were considered adults. The three animals that required a supplementary dose were on average 4.96 kg, and so underdosing does not explain their limited clinical response.

Safety, reliability, reversibility, volume and availability considerations formed the basis for protocol selection. Dose rates for each protocol were chosen based on a literature review performed at the time of the study (2016) [12,23,37–39]. The higher dose of 10 mg/kg ketamine in the KX protocol relative to 5 mg/kg in KM/KD was selected following a review of a previous study showing that different ratios of ketamine–xylazine combinations affect duration of induction, recovery and total anesthesia time, and that relatively high doses of xylazine have been associated with reduced thermoregulatory capacities [7].

Atipamezole dose rates in the KM and KD groups reflected those licensed for use when antagonizing medetomidine and dexmedetomidine in domestic animals. Atipamezole has been used successfully in chimpanzees (*Pan troglodytes*) at 0.15–0.2 mg/kg to reverse comparable doses of KM to those described here [38]. Higher doses of atipamezole than those reported in this study have been used to reverse KM and KD protocols in cynomolgus macaques (*Macaca fascicularis*), i.e., 0.25 mg/kg and 0.5 mg/kg, respectively [40,41]. Atipamezole is not marketed for use as an antagonist for xylazine, but has been used successfully at doses of 0.1 or 0.2 mg/kg in olive baboons (*Papio anubis*) following KX administration [42]. While the atipamezole dose of 0.06 ± 0.02 mg/kg administered in the current study appears significantly lower, the xylazine dose administered was also lower, and so the ratio of atipamezole: xylazine is comparable between these two studies (0.2:1 vs. 0.2–0.4:1) [42].

Although induction time was longer with KX than KM or KD, it was comparable to that reported in another study where KX was used at similar doses [7]. Recovery time for KX was also longer than KM/KD. Total duration of immobilization was also significantly

greater in the KX group because of longer induction/recovery; mean procedure time did not differ significantly between groups. It is suspected that a relatively high ketamine and low α-2 agonist dose (most pronounced with KX) are responsible for the observed longer induction times (KM and KX), and that the extended recovery times may be attributable to a combination of the relatively high ketamine dose, along with the relatively low atipamezole dose (again, both most pronounced in KX). It is also worth noting that the procedure time in our study was very short and so it is likely that the effects of the high ketamine dose would still be present at the time of atipamezole administration.

Across all protocols, increasing total dose had minimal impact on the speed of induction, but significantly increased recovery time, suggesting that accurate estimation of bodyweight, or ideally obtaining an actual bodyweight wherever possible, is important.

Mean resting HR in conscious rhesus macaques has been reported as 110 ± 11.51 bpm [5], comparable to the single point HR measurements recorded in this study, and to previous studies on Japanese macaques (*Macaca fuscata*) anesthetized with KM [20]. Previous studies have identified that α-2 agonist–ketamine combinations used in primates depress the HR and RR more than the administration of ketamine alone [6,31,34,42]. HR and RR were not correlated with dose rate in the current study; the KX group had a higher mean HR and lower mean RR than KM/KD, but this difference was not statistically significant. In a comparison of KM and KD in golden-headed lion tamarins (*Leontopithecus chrysomelas*), HR progressively decreased 15 min after drug administration in both protocols, and was significantly lower in the KD than the KM group at 15 and 45 min post drug administration [6,43]. In the current study, there was a significant positive relationship between total induction dose and RR in both the KM and KX groups; this was not observed in the KD group and the reasons for this are unclear.

Hypoxemia of potential clinical significance has been identified in macaques under KM and KX anesthesia [6,20,42]. Although only single point HR and RR measurements were obtained here due to the short duration of the procedure, based on other studies, it is likely that HR, and maybe also RR, would have decreased over time, although clinically relevant effects are usually reversed following atipamezole administration [9,20,25,34,40,42,43]. Nevertheless, recovery times were long and supplemental oxygen provision and further monitoring, such as pulse oximetry, would likely have been beneficial during this period.

Sedation scores for KM and KD were similar (mean 2.13 and 2.15, respectively), and both were higher than KX (mean 1.81), although this was not statistically significant. In most cases, animals were sufficiently immobilized for handlers to undertake required procedures safely and effectively. However, almost 10% of KX group animals (3/31) and 1/31 in the KM group were not considered safe enough for vital parameters to be obtained. In these cases, animals may have been removed from the squeeze cage before induction agents were fully effective; or they were true spontaneous recoveries, as previously reported when using KM and KX in macaques [34,41].

Based on the reliable response observed in the majority of macaques anesthetized with KM, it is suspected that the single animal in this group that failed to show any appreciable response to the induction dose had either inadvertently not received the dose, or it had been administered into the subcutaneous space, where absorption of α-2 agonists is unpredictable [6].

Sedation score was dose-dependent across all protocols, with increased doses resulting in higher sedation scores; this was most pronounced in the KD group. This indicates that sedation efficacy with KD is more closely correlated to dose rate than in the KM/KX protocols described here, further supporting the benefit of known pre-anesthetic bodyweights.

No adverse physiological or behavioral effects were recorded in the current study or during the seven-day period following anesthesia, and macaques were able to be immedi-

ately reunited with conspecifics after recovery, supporting the suitability of these protocols in zoo, safari park and field settings.

It is often recommended that reversal of α-2 agonists is best undertaken 20 min or longer after administration of ketamine protocols, due to the potential for residual ketamine sedation [23,44], although whether excitement after reversal of α-2 agonist–ketamine protocols is problematic in primates has been questioned [41]. Procedure time in this study was short, with atipamezole being administered no more than 11 min post induction dose, and yet no ketamine associated emergence delirium was observed, supporting previous findings [25].

The authors emphasize that these protocols alone are unsuitable for procedures that are anticipated to elicit pain lasting beyond the duration of the immobilization; atipamezole also reverses the analgesic effects of the α-2 agonist [40], and ketamine action is short-lived, so additional analgesics would be required in such cases.

This study had several limitations. The anesthetist was not blinded to the protocol being used, which potentially introduced a degree of bias to the sedation scores assigned.

Due to the very brief nature of the clinical procedure, only single-point HR and RR were obtained, and no additional cardiovascular system monitoring was undertaken. Trends were not identified, and the physiological effects of protocols were largely unstudied. The absence of rectal temperature monitoring meant that it was not possible to ascertain if the animals were normothermic, and therefore to assess any effect of hypothermia on the recovery times for each macaque.

The higher ketamine dose in the KX group when compared to KM/KD meant that direct comparisons of the effects of the three α-2 agonists could not be evaluated. However, these data were obtained opportunistically as part of a routine management procedure and not primarily as an experimental study. Therefore, dose rates were chosen on the basis of expected reliability and safety such that the procedure could be completed successfully.

Atipamezole was administered once procedures were completed, so the duration of effect of each combination could not be assessed. Comparisons between sexes were not made because there were so few males, and only one male was considered fully mature. Additionally, as macaques were managed as a group, ages were unknown, so the effects of protocols on different age classes were not evaluated. The population pre-anesthetic weights were not obtained, but this is generally consistent with large troops of managed primates and field settings. Since medetomidine and dexmedetomidine are essentially the same agent, the fact that few differences were observed between the KM and KD protocols was unsurprising. However, the results of this study indicate that while KM and KD were comparable, the KD protocol provided more rapid induction and recovery times with the most reliable sedation scores when used in rhesus macaques for minor procedures. The KX protocol used in this study produced prolonged induction and recovery times and poorer sedation scores, with 10% of animals considered unsafe for personnel to perform all required procedures. However, in situations where xylazine is the only α-2 agonist available, the authors suggest that a reduction in ketamine and increase in atipamezole doses may reduce recovery times, and an increase in xylazine dose may be considered to improve degree of sedation [45,46]. An increase in atipamezole dose may also decrease recovery times when using KM and KD.

5. Conclusions

As hypothesized, the KM and KD protocols used provided more rapid and reliable sedation than the KX protocol at the doses described. In contrast to the hypothesis, whilst the KM and KD protocols provided safe and effective immobilization for minor procedures in macaques, response was less reliable with the KX protocol.

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