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Research article

Dose-dependent effect of romifidine on intraocular pressure in clinically healthy buffalo (*Bubalus bubalis*)

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ABSTRACT

In the present study, changes in intraocular pressure (IOP) associated with romifidine sedation in buffalo were evaluated. Eighteen healthy adult, non-pregnant, buffalo without ocular abnormalities were used in a prospective randomized trial. Buffalo were allocated into three groups (six each). Buffalo in the treated groups received an intramuscular injection (IM) of romifidine at 40 or 50 μg/kg. The control group was administrated an equivalent volume of sterile saline (0.9% NaCl; 0.4 ml/100 kg). Baseline IOP (T0) values were obtained using applanation tonometry. Immediately afterwards, romifidine was administered and IOP values of both eyes were measured at 5, 15, 30, 45, 60, 90, 120, and 180 min post-administration. The pre-administration values (T0) of IOP for both the left and right eyes ranged from 30-36 (mean, 33 ± 1.5) mmHg and 30–35 (mean, 33.7 ± 1.4), respectively. IOP values decreased significantly after administration of both doses of romifidine compared with the placebo ($P < 0.01$). Compared with the control, the IOP decreased significantly in animals treated with both doses from 5-90 min post-administration in both eyes ($P < 0.05$). In the right eye, the lowest IOP value in the romifidine treated groups was observed at T30 (21.6 ± 1.0 and 23.3 ± 1.4 mmHg), respectively. In the left eye, the lowest IOP was observed at T60 (22.5 ± 3.0 and 23.3 ± 2.8 mmHg), respectively. In conclusion, romifidine could be recommended as an alternative analgesic in buffalo, especially for ocular affections associated with increased IOP. A dose of 40 μg/kg could be used at a low cost.

1. Introduction

Sedation is recommended for the restraint of buffalo in order to perform various types of surgery, especially when a standing position is required (Fierheller et al., 2004; Lee and Yamada, 2005; Marzok and El-khodery, 2017). In contrast, under field conditions, a general anesthesia is not appropriate for large ruminants due to the lack of facilities and high cost of the equipment (Fierheller et al., 2004; Marzok and El-khodery, 2017). Moreover, recumbency associated with general anesthesia may place great stress on the cardiovascular and pulmonary functions (Marzok and El-khodery, 2017).

Cattle sedation is usually achieved using α-2 adrenoceptor agonist drugs (Lin and Riddell, 2003; Marzok and El-khodery, 2017). Romifidine is an imidazole derivative, selective α-2 adrenoceptor agonist with analgesic and systemic effects. Its sedative and antinociceptive effects have been evaluated after epidural, spinal or systemic administration in large and small ruminants (De Segura et al., 1993; Prado et al., 1999; Amarpal et al., 2001; Amarpal Kinjavdekar et al., 2002; Fierheller et al., 2004; Kinjavdekar et al., 2006; Marzok and El-Khodery, 2009; Marzok and El-khodery, 2017). Romifidine is superior to other α-2 adrenoceptor agonists because it has a long lasting analgesic effect with minimal ataxia (Clarke et al., 2014). However, it has been reported to lead to a significant decrease in intraocular pressure (IOP) in clinically normal horses (Marzok et al., 2014). A decrease in IOP has also been reported during the evaluation of the clinical effects of α-2 adrenoceptor agonist (medetomidine) in small animal practice (Sinclair, 2003).

The measurement of IOP, or tonometry, is an important step during routine ophthalmic examination, especially for the diagnosis and monitoring of various ocular disorders (Gum et al., 1998; Ofri et al., 1998; Komáromy et al., 2006; Pamuk et al., 2011; Marzok et al., 2014).

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Although data on IOP and tonometry in normal cattle are available (Gum et al., 1998; Gerometta et al., 2004), there are few reports on IOP changes associated with disease conditions in cattle (Andrade et al., 2013; Pearce and Moore, 2014).

Although the disease conditions with various ophthalmic lesions in domestic buffalo have been studied (Osman and Al-Gaabary, 2007; Munang'andu et al., 2011), the reference values for IOP, along with the references of other ophthalmic variables and diagnostic tests are limited (Pamuk et al., 2011). Moreover, the effects of α-2 agonists on IOP in clinically healthy adult buffalo have not been evaluated to date.

The aim of the present study was therefore to investigate the dose-dependent effects of romifidine on IOP in clinically normal buffalo.

2. Materials and methods

2.1. Buffalo

Eighteen healthy adult non-pregnant buffalo were used in the study. The age and body weight ranged from 3.5-7 years and 380–600 kg, respectively. All buffalo were kept on a private farm in Dakahlia Government, Mansoura, Egypt in individual free stalls (4.5 × 4.5 m) on straw bedding which was changed once daily. Buffalo were milked twice (early morning and evening) and were fed with a diet based on hay and concentrates according to maintenance. The buffalo had free access to water.

In order to include healthy animals, all the buffalo underwent a complete physical examination and a blood sampling for complete blood count (CBC). Blood samples were collected by the tail vein puncture directly into an ethylenediaminetetraacetic acid (EDTA) tube. Immediately after collection, blood samples were kept cooled (-4 °C) and transported to the laboratory for analysis.

Eyes were considered normal based on visual observation of the eyelid, conjunctiva, and cornea as well as the results of the Schirmer tear test. The clinical and ophthalmic examinations were carried out by a single individual who was blinded to all treatment groups.

2.2. Study design

The experimental protocol of the current study was approved by the Animal Care Committee of Mansoura University, in accordance with Egyptian ethical codes for studies on experimental animals. Buffalo were randomly allocated into three groups (six buffalo each). Group 1 received an IM romifidine (Sedivet; Boehringer Ingelheim, Vetmedica GmbH, Ingelheim/Rhein, Germany) at a dose of 40 μg/kg. While the second group received romifidine at a dose of 50 μg/kg. Animals in the third group received normal saline (0.9% NaCl; 0.4 ml/100 kg IM; El Nasr Pharmaceutical Company, Cairo, Egypt).

In all groups, the IOP of both eyes was measured and recorded by the same investigator and during the same work session. The measurements were recorded immediately before the administration of romifidine or saline (T0), and then at 5 (T5), 15 (T15), 30 (T30), 45 (T45), 60 (T60), 90 (T90), 120 (T120), 150 (T150) and 180 (T180) minutes post-administration. Heart rate (HR, beat/min) and respiratory rate (RR, breath/min) were assessed for each buffalo at each time point. Ocular rotation was also evaluated according to the method described in the literature (Greene, 2003).

2.3. Measurement of IOP

All experiments were performed outdoors in a quiet environment in natural daylight, and the buffalo were restrained by the same assistant. First, to facilitate the opening of the upper eyelid, 4 ml lidocaine hydrochloride (Debocaine, 20 mg/ml, Aldebiky, Egypt) was infused subcutaneously along the dorsal zygomatic arch of each eye to block the palpebral branch of the auriculopalpebral nerve. The head was maintained in a normal upright position during all IOP measurements. All measurements were obtained in the morning to reduce individual and diurnal variations. Eyes were examined in a random order (left *vs* right) in each buffalo. Gentle manipulation of the eyelids was carried out to prevent pressure on the globe. Topical anesthesia of the cornea of both eyes was performed using 0.2 ml of 0.5% proparacaine solution (Alcaine; Alcon Laboratories, INC, Fort Worth, TX, USA) before IOP measurement using an applanation tonometer (Accu-Pen, Accutome, INC, Phoenixville Pike, Malvern, PA, USA). According to the manufacturer's instructions, the tonometer was factory calibrated before the study, and only IOP readings with a 5% variance (5% displays on Acuu-Pen) were recorded.

Measurements of IOP were obtained by gently touching the central aspect of the cornea at 5 s intervals, after which each the IOP reading was averaged from the mean of three sequential measurements.

2.4. Data analysis

The data analysis was performed using the SPSS statistical software program (SPSS for Windows, version 16.0; SPSS Inc., Chicago, IL, USA). Initially, data were assessed for normal distribution by the Kolmogorov–Smirnov test and were found to be normally distributed. Consequently, the mean and standard deviation for each variable were calculated at each time point. The homogeneity among the three groups at the first examination time was evaluated using the Kruskal-Wallis test. As the measurement was found to be homogenous, the main effects of time and treatment were determined using the general linear model with ANOVA repeated-measures. The results of the time effect and time × treatment interaction were evaluated out using Wilks' lambda test. When Wilks' lambda test was significant, one-way ANOVA with the post hoc Duncan multiple variable test was applied to detect any differences between groups. Results were considered significant at $p < 0.05$.

3. Results

All the animals were considered healthy based on physical examination and CBC results (Table 1). The mean body weight at inclusion was 429.18 ± 47.30 kg for Group 1, 494.38 ± 70.40 kg for Group 2, and 526.75 ± 80.56 kg for Group 3. All experimental procedures were conducted successfully without any observed ocular irritation or signs of pain during application of the applanation tonometry.

Table 1. Complete blood count (CBC) values, expressed as mean and standard deviation, evaluated in three different groups (Group 1 - Romifidine 40 μg/kg; Group 2 - Romifidine 50 μg/kg; Group 3 – Saline: 0.9% NaCl) composed of 6 buffalo (*Bubalus bubalis*) each, for a total of 18 animals.

Parameter	Group		
	Group 1	Group 2	Group 3
RBCs count ($x10^{12}$/l)	6.33 ± 0.81	5.66 ± 0.87	5.53 ± 0.74
HGB (g/l)	115.20 ± 12.80	111.10 ± 10.60	110.10 ± 10.90
PCV (%)	34.05 ± 2.80	37.08 ± 3.01	33.08 ± 2.70
MCV (fl)	56.50 ± 5.01	57.70 ± 4.71	54.60 ± 4.44
MCH (pg)	16.93 ± 2.10	19.41 ± 1.72	18.79 ± 1.50
MCHC g/dl	33.01 ± 0.90	31.22 ± 2.00	30.02 ± 1.05
WBC ($x10^9$/l)	10.50 ± 1.59	11.40 ± 2.22	9.30 ± 1.82
PLT ($x10^9$/l)	155.30 ± 51.40	174.11 ± 67.40	149.00 ± 47.90
Lymphocytes count ($x10^9$/l)	7.51 ± 2.51	6.81 ± 2.13	5.72 ± 1.53
Neutrophils count ($x10^9$/l)	3.10 ± 1.33	2.88 ± 0.84	2.90 ± 0.93
Eosinophils count ($x10^9$/l)	0.09 ± 0.03	0.06 ± 0.02	0.08 ± 0.04
Monocytes count ($x10^9$/l)	0.51 ± 0.22	0.62 ± 0.19	0.43 ± 0.12

Legend: Red blood cell (RBC) count, hemoglobin concentration (HGB), packed cell volume (PCV), main corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), total white blood cell count (WBCs), platelet count (PLT).

The pre-administration values (T0) of IOP for both the left and right eyes ranged from 30-36 (mean, 33 ± 1.5) mmHg to 30–35 (mean, 33.7 ± 1.4), respectively. The pre-treatment normal values (T0) of IOP in all groups were homogenous and did not show any significant variations (Figures 1 and 2).

Based on treatment × time interaction, a significant decrease in IOP values was observed after the administration of both doses of romifidine compared with the placebo (Wilks' lambda test for treatment × time interaction, $P < 0.01$). For both doses of romifidine, the IOP decreased significantly from 5-90 min post-administration in both eyes compared with the control ($P < 0.05$). The lowest value of the left eye in the romifidine-treated groups (40 μg/kg and 50 μg/kg) was observed at T60 (22.5 ± 3.0 and 23.3 ± 2.8 mmHg), respectively. While the lowest IOP level of the right eye was observed at T30 (21.6 ± 1.0 and 23.3 ± 1.4 mmHg), respectively.

In buffalo treated with romifidine at 40 μg/kg, the IOP started to return to the normal level earlier than those treated with 50 μg/kg (120 *vs* 150 min post-treatment for both eyes).

Based on the time × dose interaction, there was a significant decrease in heart rate (Wilks' lambda test for time × treatment interaction, $P < 0.01$) and respiratory rate (Wilks' lambda test for time × treatment interaction, $P < 0.01$). The dose-dependent effect of romifidine on the heart rate was evident at T120-180 (Figure 3). However, romifidine did not induce a dose-dependent effect on the respiratory rate (Figure 4). There was no ocular rotation in any of the buffalo treatment groups at any time points.

4. Discussion

Romifidine is not commonly used as a sedative for buffalo in clinical practice. However, its sedative and analgesic effects in normal buffalo have been evaluated (Marzok and El-Khodery, 2016). Although its adverse clinical effects have been reported in bovine and equine species (Kullmann et al., 2014; Interlandi et al., 2017), its effect on IOP has only been studied in horses (Marzok et al., 2014). The aim of this study was to therefore evaluate the dose-dependent effect of romifidine on IOP in normal adult buffalo.

The two variables that may increase IOP measurements are manipulation of the eyelids or periorbital tissues and stress. In the present study, minimizing manipulation whilst obtaining the IOP values was achieved through auriculopalpebral nerve blockage of each eye to facilitate the opening of the eyelids. Previous studies on equine species have suggested that auriculopalpebral nerve block has no significant effect on IOP (Gilger et al., 1995), while a slightly overestimated IOP might occur when the auriculopalpebral nerve block is not used (Wilkie, 2010; Stine et al., 2014). The nerve block may therefore be recommended for this purpose in buffalo as this species is more difficult and dangerous to handle.

Proparacaine, which is a topical local anesthesia that was used in the present study, is preferable for IOP measurements (Stine et al., 2014). However, tetracaine, another very commonly used topical anesthetic, has been found to lead to a drop in IOP (Sarchahi and Bozorgi, 2012). In our experience, buffalo do not remain stable during manipulation; therefore successful eye tonometry entails restraining the animals and using a topical application of anesthetics. The recommended dose of romifidine in large ruminants is 30–60 μg/kg. Here, the two doses chosen (40 and 50 μg/kg) were based on the results of a previous pilot study, in which lower doses did not induce acceptable analgesia and higher doses induced a marked recumbency (Marzok and El-Khodery, 2016; Marzok and El-khodery, 2017). In addition, it was assumed that most buffalo would not tolerate frequent sequential measurements of IOP at nine time points over 180 min without adequate sedation. Although this sedation level was not evaluated in this study, the majority of buffalo were managed very easily and tolerated the application and tonometry measurement well.

In the present study, IOP measurements were carried out at a fixed time in day light as the time of the day has previously been shown to affect the measurement of IOP in cats (Del Sole et al., 2007).

In the present study, IOP decreased significantly at T5, T15, T30, T45, T60 and T90 compared to the controls for both doses of romifidine administered. The precise cause of the decrease in IOP after romifidine administration in buffalo is unexplained. However, the theories explaining the mode by which the romifidine and other α2-adrenorecptor agonists exert their effect on IOP in horses have been extensively discussed (Lowe and Hilfiger, 1986; LeBlanc, 1991; Marzok et al., 2014; Stine et al., 2014). It is well known that romifidine produces a longer sedative and analgesic effect in horses than the other α-2 adrenergic agonists. The sedation obtained with romifidine in buffalo lasts for 30–120 min (Marzok and El-Khodery, 2016). Many ocular procedures require a longer duration of sedation and analgesia; therefore, we assessed the effect of romifidine on IOP in buffalo for 180 min post administration.

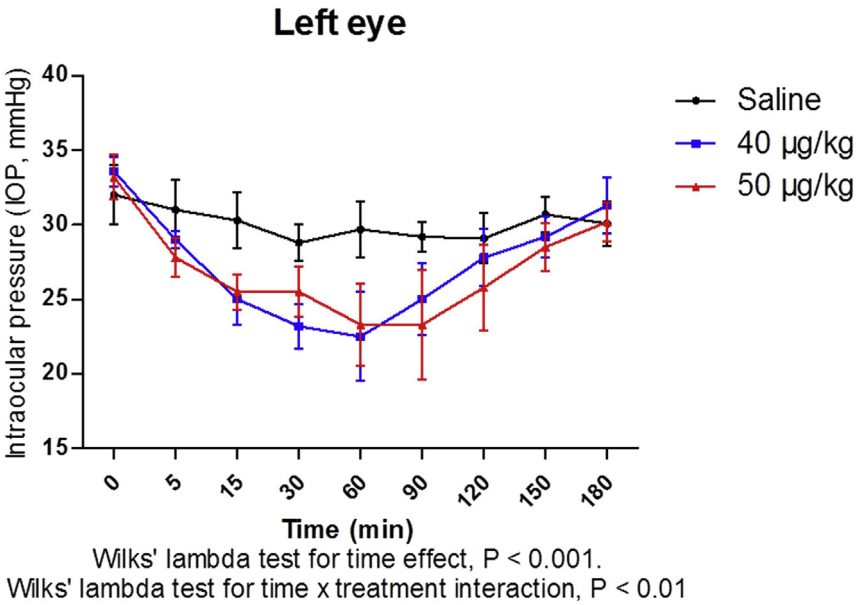

Figure 1. Effects of romifidine (40 and 50 μg/kg) and saline (0.4 ml/100 kg) on intraocular pressure (IOP, mmHg, mean ± SD) of left eyes in 18 adult buffalo.

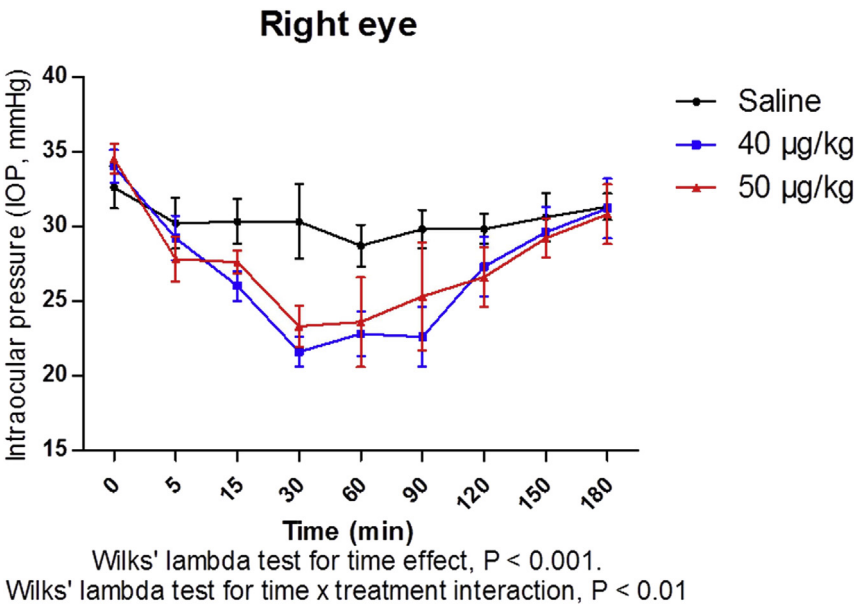

Figure 2. Effects of romifidine (40 and 50 µg/kg) and saline (0.4 ml/100 kg) on intraocular pressure (IOP, mmHg, mean ± SD) of right eyes in 18 adult buffalo.

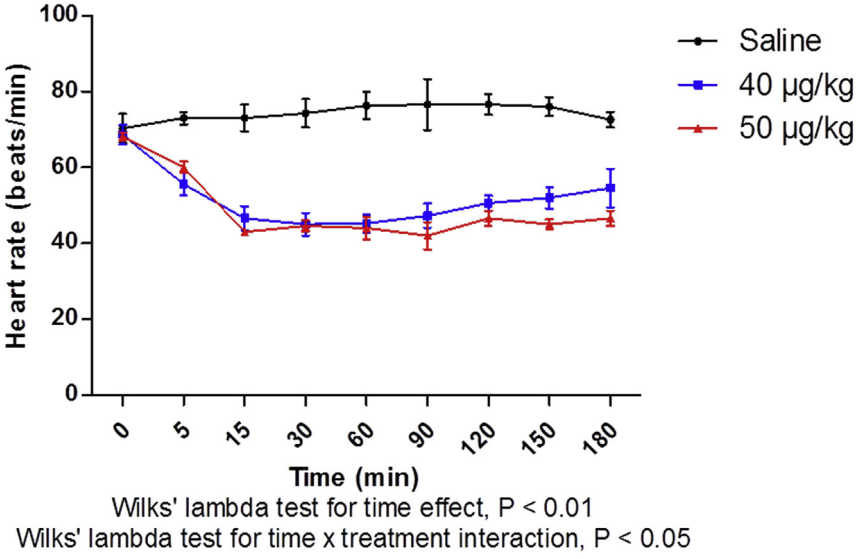

Figure 3. Effects of romifidine (40 µg/kg and 50 µg/kg) and saline (0.4 mL/100 kg) on heart rate (HR, beat/min, mean ± SD) in 18 adult buffalo.

At T30 post-administration, a non-significant decrease in the IOP in 40 µg/kg was detected in comparison with the other dose. Although there was no significant variation between the two doses, we cannot rule out that there might have been a dose-dependent effect of romifidine on IOP. At the clinical level, Marzok and El-Khodery found that epidural romifidine administration at three doses (30, 40 and 50 µg/kg) showed a dose-dependent anti-nociceptive and sedative effect in cattle, where profound sedation and analgesia were achieved with a dose of 50 µg/kg (Marzok and El-Khodery, 2016). A low dose of romifidine was therefore initially recommended from the Authors, followed by an increase in the dose until the desired effect was obtained.

Romifidine at both doses produced a significant decrease in heart rate. The dose dependent effect was recorded at T120-T180. This result is in agreement with a previous study of epidurally administered romifidine in buffalo (Marzok and El-khodery, 2017). Bradycardia has been found to occur after an alpha-2 adrenoreceptor agonist injection due to central stimulation of the vagus nerve (Clarke et al., 2014). A significant decrease in respiratory rate was also recorded in our study, which could be attributed to the sedative effect of romifidine. This result is in accordance with that recorded after romifidine administration in goats and cattle (Fierheller et al., 2004; Kinjavdekar et al., 2006). In contrast, a non-significant alteration in the respiratory rate has been observed after epidural administration of romifidine in buffalo (Marzok and El-Khodery, 2016).

The present study has some limitations. First, there were no available reference values for IOP in water buffalo which are crucial for a correct diagnosis of ocular disorders in various species. Therefore, in the present study, the T0 measurements were considered as being approximately the normal values. Interestingly, the pre-treatment measurements of IOP in our study were higher than those observed in Anatolian buffalo (Pamuk et al., 2011), suggesting inter-species variations in IOP values. Secondly, we did not observe any differences between the two doses of romifidine used, and could not establish a dose-dependent effect of romifidine on IOP. A wider dose range should be therefore considered in future studies. Finally, we need to expand our research to study the sedative effect of romifidine on other physiological and behavioral variables in buffalo. We also need to determine the correlation between those variables and

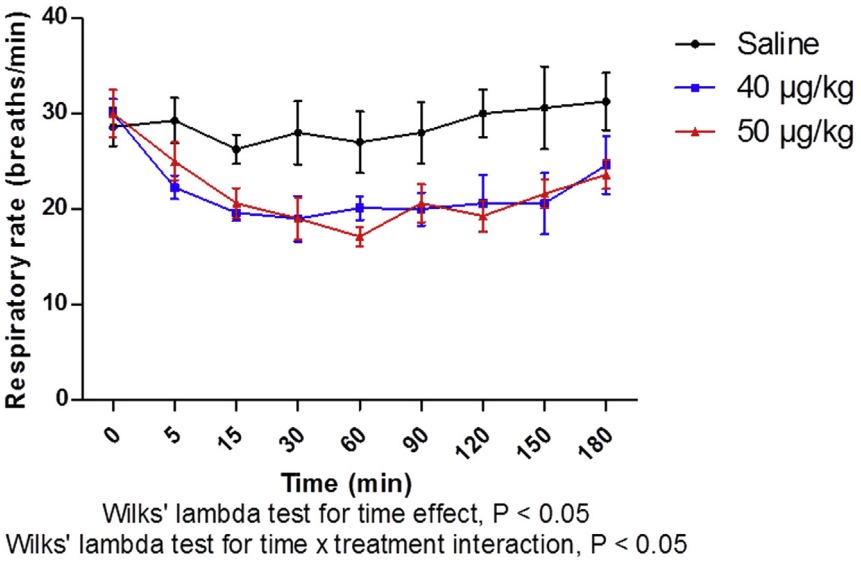

Figure 4. Effects of romifidine (40 µg/kg and 50 µg/kg) and saline (0.4 mL/100 kg) on and respiratory rate (RR, breath/min, mean ± SD) in 18 adult buffalo.

changes in IOP at different time points which could provide a basis for the clinical use of romifidine in buffalo.

5. Conclusions

Romifidine is recommended as an alternative sedative and analgesic agent for surgical interventions in buffalo, especially for ocular infections associated with increased IOP as it provides a dual benefit by providing sufficient analgesia and decreased IOP. In addition, as there were no differences observed in IOP between the two doses used, the low dose (40 µg/kg) is recommended for economic reasons.

Declarations

Author contribution statement

A. Rizk: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

K. Abouelnasr, S. El-Khodery, M. Tagawa: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

F. Bonelli: Analyzed and interpreted the data; Wrote the paper.

I. Nocera, A. Briganti: Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Competing interest statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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