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Original Research

Comparative Effect of Intravenous Administration of Medetomidine, Tramadol, and Medetomidine/Tramadol Combination on Intraocular Pressure (IOP) in Clinically Healthy Donkeys (*Equus asinus*)

Mohamed A. Hamed [a], Mohamed Abdo Rizk [b], Ahmed Hafez [c], Abdel Salam El–Mahdi [d], Sabry Ahmed El-khodery [b,*]

[a] Department of Surgery, Anesthesiology and Radiology, Faculty of Veterinary Medicine, Aswan University, Aswan, Egypt
[b] Department of Internal Medicine and Infectious Diseases, Faculty of Veterinary Medicine, Mansoura University, Mansoura, Egypt
[c] Department of Pharmacology, Faculty of Veterinary Medicine, Aswan University, Aswan, Egypt
[d] Department of Ophthalmology, Faculty of Medicine, Zagazig University, Zagazig, Egypt

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ABSTRACT

In this study, an analysis of the comparative effect of intravenous medetomidine, tramadol, and medetomidine combined with tramadol on the intraocular pressure in donkeys was conducted. In an experimental randomized prospective study, 24 adult donkeys devoid of ophthalmic defects were allocated randomly into four groups (six each). The first group received medetomidine hydrochloride (MED) intravenously at 0.007 mg kg^{-1}, and the second group received tramadol hydrochloride (TRA) at 2 mg kg^{-1}. The third group received a combination of MED and TRA at the same dose rates. However, the fourth group received 10 mL of 0.9% normal saline. Intraocular pressure values, heart rate, respiratory rate, and body temperature were measured before treatment (T0) and at 5, 15, 30, 45, 90, and 120 minutes after treatment. Donkeys treated with MED alone or MED/TRA combination exhibited a significant ($P < .05$) decrease in heart rate and respiratory rate at T5 until T90 compared with tramadol and normal saline. Intraocular pressure significantly ($P < .001$) decreased in donkeys treated with MED or MED/TRA combination in comparison with TRA and normal saline at T5 to T90. The highest reduction in IOP values in both treated groups was observed at T30 in the right and left eyes ([11.30 ± 0.94 and 10.59 ± 0.51 mmHg, MED groups, respectively] and [12.80 ± 0.65 and 12.30 ± 0.58 mmHg, MED/TRA groups, respectively]). In conclusion, medetomidine alone or in combination with tramadol could decrease the IOP values in healthy donkeys. Therefore, it may be used safely as a preoperative analgesic for intraocular surgery.

1. Introduction

Measurement of intraocular pressure (IOP) in the equine is a part of recommended complete ophthalmic examination, especially in referral clinic [1]. Intraocular pressure is the pressure of intraocular aqueous humor on the eye's fibrous layer and can be determined by applanation tonometry [2], which is required for examination of horses suffering from focal or diffuse corneal edema, red or painful eye, orbital trauma, lens luxation, glaucoma, and uveitis [2–4]. To avoid false results, measurement of IOP in horses is recommended to be applied with the horse's head in normal position [5]. Interestingly, extremely tight closure of the eyelids can falsely elevate IOP values and make the measuring process extremely difficult [6]. Fortunately, application of auriculopalpebral nerve block does not alter IOP significantly [7]. However, anesthetic agent can affect IOP reading in inpatient animals, thus this effect be taken into account [8].

Alpha-2 adrenoceptor agonists are routinely used in ophthalmic procedures in equines [9,10]. Alpha-2 adrenoceptor agonists, xylazine, detomidine, and romifidine, have been found to decrease

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* Corresponding author at: Sabry Ahmed El-khodery, Department of Internal Medicine and Infectious Diseases, Faculty of Veterinary Medicine, Mansoura University, Mansoura 35516, Egypt.
E-mail address: khodery@mans.edu.eg (S.A. El-khodery).

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the IOP in horses [7,11,12]. The effect of medetomidine and combination of medetomidine with opioids on IOP in pets has been described [13–15].

Intravenous (IV) administration of medetomidine in dogs (1500 μg m^{-2}) had no pronounced effect on IOP [15]. However, a combination of 300 μg m^{-2} medetomidine and 6.0 mg m^{-2} butorphanol intravenously induced a transitory increase followed by consequent decrease of IOP [14]. Moreover, administration of intramuscular medetomidine (80 μg kg^{-1}) induced a significant decrease in IOP in dogs, which was observed at 6 hours after administration [16].

Tramadol, an analog of codeine, is a synthetic centrally acting analgesic drug [17]. Dogs that received tramadol hydrochloride (TRA) intramuscularly (4 or 6 mg/kg^{-1}) during intraocular surgery showed no noticeable changes in IOP [18]. Nevertheless, the impact of medetomidine or tramadol on IOP in the donkey has not been studied. Thus, the aim of this prospective study was to investigate changes in IOP associated with clinically effective doses of medetomidine, tramadol, and medetomidine/tramadol combination in clinically healthy donkeys.

2. Materials and Methods

2.1. Donkeys and Clinical Examination

Twenty-four adult donkeys (14 geldings and 10 mares) were included in a randomized prospective study. The age of donkeys ranged from 5 to 8 years, and the weight ranged from 130 to 180 kg. Before the experiment, all donkeys underwent a general physical examination and biochemical analysis to ensure that they were healthy and free from concurrent systemic disease. The present investigation was approved by the Animal Care Committee of the Mansoura University, in accordance with Egyptian ethical codes for studies on experimental animals (approval number 04-017).

2.2. Study Design

Before each measurement, all animals received ad libitum access to food and water. Donkeys were considered normal on the basis of complete ophthalmic examination with the Schirmer tear test, slit lamp biomicroscopy, and indirect ophthalmoscopy. The donkeys had not received any ocular medication for at least 2 weeks before the experiment. The donkeys were randomly allocated into four groups (six each). First and second groups were treated with intravenous medetomidine hydrochloride (MED, 1 mg/mL, Domitor; Orion Pharma Animal Health, Kvistgard, Denmark) at a dose rate of 0.007 mg/kg [19,20] and TRA (100 mg/2 mL, Koralodol; Amriya Pharm, Egypt) at a dose rate of 2 mg kg^{-1}, respectively [21,22]. Combination of both drugs was administered to the donkeys in the third group at the same dose rates, whereas donkeys in the fourth group received 10 mL of 0.9% normal saline (AL-Mottahedoon Pharma Co, 10th of Ramadan, Sharkia, 137, Egypt) and served as a placebo control. All drugs were adjusted to a 10 mL final volume by adding the saline solution. Medetomidine was given as a bolus, whereas tramadol was slowly injected over at least 2 minutes as recommended by the manufacturer instructions. Intraocular pressure (mmHg), heart rate (beats/min), respiratory rate (number/min), and body temperature were measured at baseline preadministration (T0) and then at a 5 (T5), 15 (T15), 30 (T30), 45 (T45), 60 (T60), 90 (T90), and 120 (T120) minutes after administration. This study was applied in a typical indoor inaudible environment, and the same handlers have provided restraint of the animal and measurement of IOP in all groups.

2.3. Intraocular Pressure Measurement

Intraocular pressure was measured by an applanation tonometer (Accu-Pen; Accutome Inc Phoenixville Pike, Malvern, PA, USA). Before tonometry, an auriculopalpebral nerve block was performed with 2–3 mL of 2% lidocaine (Debocaine; El-Debeki Co for Pharmaceutical & Chemicals Industries, Egypt) to facilitate the opening of the upper eyelid. Before IOP measurements, the head of the animal was maintained in a normal and upright position, by placing the mandible of the examined animal on the shoulder of one of the investigators for at least 2 minutes and proceeding to measurement at all time points to give an adequate period for normalization of IOP.

Intraocular pressure values were attained at a fixed time in each day (between 8:00 am and 11:00 am) to diminish individual and diurnal alterations. For each donkey, the examined eye (right vs. left) was selected randomly. The eyelids were handled gently to avoid compression on the globe. Before measurement, 0.2 mL of 0.5% proparacaine solution (Alcaine; Alcon Laboratories, INC, Fort Worth, TX, USA) was dropped into the cornea of both eyes to be topically anesthetized. Three measurements were obtained by a slight touch on the central aspect of the cornea at 5-second intervals, after which the readings were averaged. The tonometer was factory-calibrated before the start of the reading, and only the IOP readings with a 5% variance (5% displays on Accu-Pen) were recorded.

2.4. Statistical Analysis

All statistical analyses were conducted using the SPSS, a commercial statistical software program (SPSS for Windows, version 20; SPSS Inc, Chicago, IL, USA). At the first step, the data were checked for normal distribution using the Kolmogorov–Smirnov test. As the data were found to be normally distributed, mean and standard deviation (SD) for each variable at different time points were presented. General linear model with repeated-measures ANOVA was selected to assess the effects of time and treatment. As a result, Wilks' lambda test was recommended to determine within-group interactions and evidence of time × treatment interactions. If Wilks' lambda test revealed a statistically significant difference between treatments, one-way ANOVA with

Table 1
Heart rate (beat/min) after intravenous administration of medetomidine (0.007 mg kg^{-1}), tramadol (2 mg kg^{-1}), medetomidine/tramadol combination (0.007 mg kg^{-1} and 2 mg kg^{-1}, respectively), and 0.9% normal saline (10 mL) in clinically healthy donkeys.

Group	Time After Treatment (Min)							
	0	5	15	30	45	60	90	120
Medetomidine (n = 6)	47.0 ± 3.1	43.0 ± 3.03^{b}	39.3 ± 3.2^{b}	36.5 ± 2.42^{b}	34.5 ± 1.8^{b}	38.3 ± 1.9^{b}	41.8 ± 2.3^{b}	47.0 ± 3.3
Tramadol (n = 6)	45.3 ± 3.4	47.2 ± 3.9^{a}	47.5 ± 3.1^{a}	47.7 ± 3.6^{a}	46.3 ± 4.1^{a}	46.8 ± 3.1^{a}	45.5 ± 3.4^{a}	46.0 ± 3.6
Combination (n = 6)	47.0 ± 3.2	43.0 ± 3.0^{b}	39.3 ± 3.2^{b}	36.5 ± 2.4^{b}	34.5 ± 1.9^{b}	38.3 ± 1.9^{b}	41.8 ± 2.3^{b}	47.0 ± 3.3
Normal saline (n = 6)	44.6 ± 3.20	44.5 ± 2.3 ^{ab}	45.3 ± 2.9^{a}	44.3 ± 3.1^{a}	43.6 ± 2.6^{a}	44.5 ± 3.0^{a}	44.6 ± 3.4^{a}	44.7 ± 3.1

Variables with different superscript letters in the same row are significantly different at $P < .05$. The obtained values represent the mean and standard deviation (SD) in each treated group at different time points. Wilks' lambda test for treatment × time interaction, $P < .05$.