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Clinical evaluation of TIVA by romifidine as a premedication, midazolam and ketamine in donkeys

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Summary

The objective of this study was to determine the clinical effects of total intravenous anesthesia (TIVA) by romifidine 0.1mg/kg as a premedication and anesthesia by intravenous injection of a mixture of midazolam 0.1 mg/kg and ketamine hydrochloride 2.2 mg/kg in the ten health She donkeys. The maintenance of anesthesia was performed by intravenous infusion of a mixture of the midazolam 0.065mg/kg/hrs and ketamine 6.6mg/kg /hrs prepared in 500ml normal saline. Data were collected just before intravenous administration of premedication (control data) and after the administration of anesthetics drugs at 5, 10, 15, 20, 25, 30, 45, 60 and 90 minutes. The clinical parameters measured included: Anesthetic Parameter (induction, anesthetic time and recovery), rectal body temperature, arterial oxyheamglobin saturation in blood (SPO2), analgesia, muscles relaxation, at the above times until the donkey responds to external stimuli. The results of the induction and maintenance of general anesthesia by this regime was found to be superior and stable. Recovery from anaesthesia was smooth and similar quality in all animals. The body temperature showed significant differences between control and 5min 37.35 ± 0.054 ;37.19 ± 0.08 ◦C with 15 min and above to the 60 min, while in SPO2 (%) the result showed significant difference ($P<0.05$) in time 90 min 97.4 ± 0.541 with 10min ; 15min 94.6 ± 1.229 ;93.7 ± 1.075 %and 20 min 93.9 ± 1.075%. There were no adverse effects noted following this anesthetic regime.

Key words:- TIVA, romifidine, midazolam, ketamine.

التقييم السريري لنظام التخدير العام الاحداث والادامة بالحقن الوريدي باستخدام الرومفدين والميدازولام والكيتامين في الحمير

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الخلاصة

هدفت هذه الدراسة قياس التأثيرات السريرية الناتجة عن استخدام برنامج التخدير العام في الحمير باستخدام الرومفدين بجرعة 0.1 ملغم \ كغم من وزن الجسم كعلاج تمهيدي ما قبل التخدير يعقبه احداث التخدير العام بحقن مزيج من الميدازولام بجرعة 0.1 ملغم \ كغم من وزن الجسم مع عقار الكيتامين بجرعة 2.2 ملغم \ كغم من وزن الجسم. تم ادامة التخدير العام بالحقن الوريدي لمزيج الميدازولام 0.065 ملغم \ كغم \ ساعة وعقار الكيتامين بجرعة 6.6 ملغم \ كغم \ ساعة ممزوجة ب 500 مل من محلول الملح الوريدي. استعملت عشرة من الحمير المحلية وتم قياس قيم المعايير السريرية قبل الحقن واعتبرت كقيم سيطرة وكذلك تم قياسها بالأوقات 5و10و 15و 20و 25و30و 45و 60 و 90 دقيقة بعد الحقن للأدوية المخدرة. شملت المعايير درجة حرارة الجسم وتشبع الدم بالاوكسي هيموكلوبين ودرجة تسكين الالم وارتخاء العضلات الهيكلية كما و تم قياس وقت احداث التخدير العام ووقت الافاقة. اظهرت نتائج التجربة ان احداث وادامة التخدير بهذا البرنامج كان فائق الجودة ومستقرة كما وان الافاقة من التخدير بهذا البرنامج كانت سلسة وبدون تعقيدات. سجل وجود فرق معنوي في درجة حرارة الجسم ونسبة تشبع الدم بالاوكسي هيموكلوبين كما لم تسجل اي تأثيرات سلبية مؤثرة في هذا البرنامج.

Introduction

The α-2-adrenoceptor agonists drugs have been recognized as worldwide use in veterinary medicine for their sedative, analgesic and muscle relaxation properties in large and small animals (1). The commonly α_2-agonists which used in veterinary practice are xylazine, detomidine, medetomidine and romifidine. Romifidine is a recent α-2 adrenoceptor agonist

marketed for use in horses (2). Romifidine has been available since 1985 (3). It has been used successfully for sedation, analgesia, and premedication in horses in several countries since 1988 (4) this drug have a dose related effect with an increase in dose resulting in an increase in their degree and duration of action (5). Romifidine can be included in analgesic and anesthetic protocols to provide additional analgesia in horses (6). Midazolam is a short-acting benzodiazepine with hypnotic, anticonvulsant, muscle-relaxant and anxiolytic properties. In clinical practice, it was using for the induction of anesthesia (7). The midazolam metabolites are conjugated and then excreted as glucuronides in the urine (8, 9). The sedative and hypnotic effects of midazolam are dose-dependent as well as dependent on route of administration; midazolam can produce maximal sedative effects in 20 minutes after intramuscular administration of 0.6 mg/kg (10). Ketamine is a phencyclidine derivative that produces a dissociative state of anesthesia. Dissociative anaesthesia was characterized by dissociation between the thalamo-cortical and limbic system on the electroencephalogram (EEG) (11and 12). Ketamine has been used as an anesthetic agent in equine medicine since the mid-70s (13). Initially, ketamine was applied just as an induction agent, producing amnesia, loss of consciousness, analgesia and immobility. In later years, based on these properties, the application of ketamine in equine anaesthesia was extended by using in different total intravenous anaesthesia protocols (14and 15).

Materials and Methods

Ten clinically healthy female donkeys weighing between 70- 100 kg aged 8-12 months have been used in this study. Romifidine was used as a premedication drug (Sedivet® 1.0%Boehringer Ingelheim Vetmedica, Inc., Spain). Midazolam (15 mg in 3 ml, Alsaad pharmaceuticals, Syria) and ketamine (kepro pharmaceuticals, 100mg/ml Holland), was used for induction and maintain the general anesthesia. The regime of general anesthesia was made by administration of romifidine at a dose of 0.1 mg/kg B.W. injected intravenously in the jugular vein as a premedication, then after five minutes, midazolam at a dose of 0.1 mg/kg B.W. and Ketamine at a dose of 2.2 mg/kg B.W. mixed in the same syringe (16) have been injected intravenously. Fifteen minutes later an infusion of midazolam 10 mg (2ml) mixed with ketamine (10ml) in 500 ml normal saline was administrated to maintain the anesthesia, the rate of dripping was 100-110 drops per minute (20 drops equal to 1ml). Temperatures and SPO2 were monitored by Omni II Touch Screen (Medical Monitor Technology from Infinium Medical USA to measure the heart rate, SPO2 (arterial oxyhemoglobin saturation) and temperature. Type and time of induction of the animals were carefully observed from the moment of premedication administration until the reflexes were disappeared to evaluate the induction type if it was smooth, shivering or struggling movements. The induction time was also recorded. The total anesthetic period between disappearance and reappearance of reflexes was recorded as anesthetic time. The nature of recovery was observed from the time of reappearance of the reflex until complete consciousness if it was smooth, staggering and difficult in standing. Analgesia was evaluated at different intervals by pin - prick method advocated according to (17) was used to evaluate the analgesic action of anesthetic combination. Muscle relaxation was evaluated depending on the flexion and extension of limbs of the donkey. The results were expressed as means (M) ± stander error (SE). Parametric data were analyzed by one ways Analysis of Variance (ANOVA) continued with Least Significant Difference (L.S.D.), and $p > 0.05$ was considered to be significant. Statistical Package for Social Sciences (SPSS) was used (18).

Results

All animals were showed signs of sedation 1-2 minutes after the administration of romifidine at dose 0.1mg/kg as a premedication, then they were anaesthetized by intravenous injection of a mixture of midazolam 0.1 mg/kg B.W and ketamine hydrochloride 2.2 mg/kg B.W that caused rapid induction within 30-60 second (Table 1). The general anesthesia time

was very smooth and provided complete unconsciousness, good analgesia, and good muscle relaxation, disappearance of all reflexes. The maintenance of the anesthesia in this study was limited for 60 minutes. The induction of anesthesia by this protocol as anesthetic agent was provided good general anesthesia in all donkeys about 20 ± 2 minutes and caused good muscles relaxation with complete unconsciousness and complete disappearance of all reflexes**.** When the infusion was stopped the recovery of the animals were smooth and ranged between 8-10 minutes, the reflexes of limbs were returned at 8 minutes, and the animals were required some effort to regain sternal recumbence for 5 minutes later (Table 1). All animals retrained to standing position without assisting.

Table (1): The time of general anesthetic regime.

Induction time second	Anesthetic time (Minutes)		Recovery time (Minutes)
	Induction	Maintenance	
30-60	20±2	60±8	8-10

All donkeys showed decrease in body temperature during the first five minutes 37.35± 0.045 followed the injection of romifidine and continuously decreased after injection of a mixture of midazolam/ketamine as anesthetic agent and up to 37.26± 0.058 at 90 minutes of observation. The statistical analysis revealed significant differences at the level of ($P<0.05$) between control and 5min with the 15, 20,25,30,45 and 60 minutes, but no significant differences ($P>0.05$) between control with 5, 10, and 90 minutes (Table 2). The effects of hypoxia are related to the degree of saturation of hemoglobin with oxygen for animals with normal hemoglobin concentration and cardiac function.SPO2 was not affected in this general anesthetic regime, the mean value within normal limit all-time. The statistical analysis revealed significant differences between 10, 15 and 20 minutes with 90 minutes, but recorded no significant differences ($P>0.05$) at zero time with all experimental time (Table2).

Table 2: Effect of general anesthesia regime on some clinical parameters in (10) donkeys.

parameter	Time minutes									
	zero	5	10	15	20	25	30	45	60	90
Body temp. (°C).	37.35± 0.054 A	37.19± 0.080 A	37.01± 0.098 AB	36.82± 0.928 B	36.67± 0.096 B	36.52± 0.112 B	36.38± 0.115 B	36.28± 0.108 B	36.19± 0.098 B	37.29± 0.058 A
SPO2 (%)	96.1± 0.737 AB	95.0± 1.229 AB	94.6± 1.212 B	93.7± 1.075 B	93.9± 1.075 B	96.3± 1.155 AB	96.0± 0.714 AB	95.7± 0.895 AB	96.9± 0.887 AB	97.4± 0.541 A

- **Value is expressed as M ± SE.**
- **Different in the capital latters refer significant differences ($P<0.05$) between time**

The combination used in this study produced excellent muscles relaxations, this muscles relaxation during anaesthesia were evidenced by relaxation of limb muscles. Muscles relaxation started at 10 minutes of experiment and extended until the signs of recovery period (Diagram). Analgesia was starting through the first 5 minutes after I.V. injection of romifidine, administration of mixture of midazolam and ketamine, which produced excellent analgesia from 15-20 minutes and continues infusion of anesthetic agents was keeping excellent analgesia in all donkeys to the end infusion at 75 minutes than gradually decrease until appear sign of recovery (Diagram).

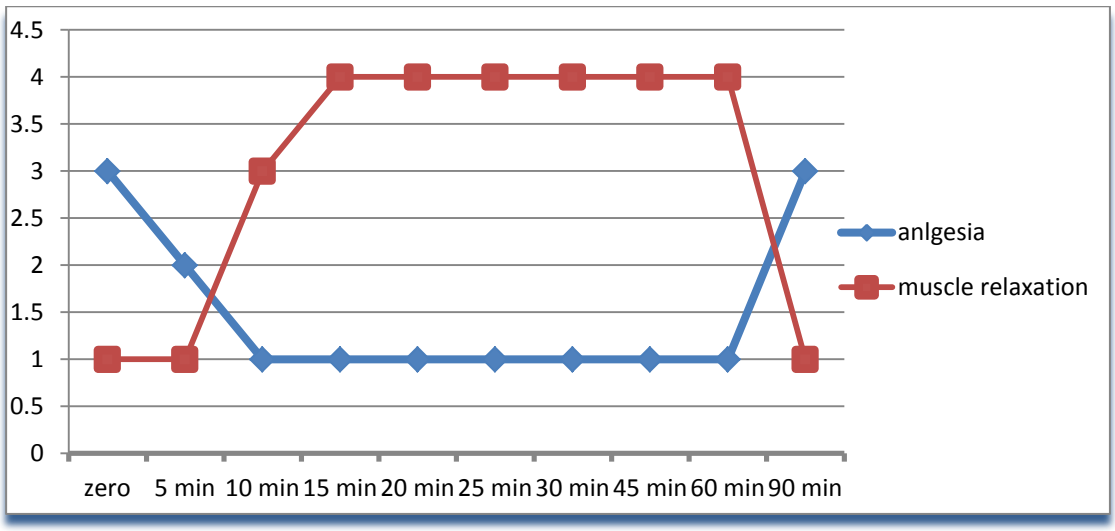

Diagram: Degree of analgesia and muscle relaxation through general anesthesia of donkeys

- **Score of analgesia(0= excellent no response, 1= good response to stimuli nystagmus created, 2= moderate purposeful movement of limbs, head or neck produced, 3= poor donkey moved into sternal position or stood)**
- **Score of muscle relaxation (4= excellent complete relaxation, 3= good adequate muscle relaxation for surgical procedure, 2= Moderate Partial relaxation of head, neck, and limb muscles, 1= Poor Rigidity in muscles of neck, head, and limbs) (27).**

Discussion

The results of sedation agreed with Carolyn, (19) which used romifidine 0.1mg/kg B.W. as a premedication and ketamine hydrochloride at a dose of 2.2 mg/kg B.W. as anesthetic agent injected intravenously in horse. On the other hand, our results coincided with (20 and 21) whom used a mixture of midazolam 0.1mg/kg B.W. as premedication and ketamine hydrochloride 2.2 mg/kg B.W. as anesthetic agent in horses. Staffieri and Driessen,(22) revealed that ketamine hydrochloride exerts its effect on CNS during induction and produces functional and electrophysiological dissociation of thalamocortical area from limbic and other subcortical structures in the brain; as a result, consciousness is lost.). All animals retrained to standing position without assisting. This result disagrees with Matthews and Taylor, (23) who found the donkeys will remain in sternal recumbence until they are quite able to stand unassisted. These animal may need (and will tolerate) a "boost" on the tail. No animal in this study retrained to recumbence after standing position. In the body temperature results agreed with the other researchers England and Clark, (24); Freeman and England, (5) who found that decreased in body temperature during general anesthesia due to reduced basal metabolic rate and muscle activity and probably the result of the effect of α-2 adrenoceptors drugs which causes depression of hypothalamic thermoregulatory center. Ketamine and other dissociative anesthetics which cause hypothermia by releasing monoamines responsible for centrally mediated hypothermia by inhibiting endogenous release of norepinephrine (25and 26). The result of SPO2 in the experimental study disagreed with Hubbel, (27) who founded the mean SPO_2 value in equine remained within 82.18 ± 5.33 and 87 ± 2.94% during surgical plain of anesthesia. On the other hand this result disagreed with Thakur *et al.* (28) who attributed hypoxemia to some drop in oxygenation probably happened like commonly seen in horses under general anesthesia because the assumption of lateral recumbence is associated with the development of ventilation-perfusion mismatches and the shunting of blood through the lungs resulting in less than optimal oxygenation. Muscles relaxation was largely attributed to the administration of romifidine and midazolam, this result agreed with (29) who used romifidine as premedication cause inhibition of neural impulses in the central nervous system and

causing inhibition of excitatory neurotransmitter release from spinal interneurons. Also Muir and Hubbell, (30), revealed that the synergetic effect of the addition of midazolam with romifidine induce deep sedation and good muscles relaxation which was evident through relaxation of muscles of the fore and hind limbs, this muscle relaxation is mainly due to inhibition of impulses at the level of central nervous system and not by paralysis of neuron muscular transmission. Ketamine itself induces poor muscles relaxation, when it used was regarded as dissociative anesthetic agent characterized by a cataleptic state in which cause strong catatonic reaction like tremor and muscle rigidity (31). Bergman, (32), suggested ketamine would be expected to be block or interfere with sensor input to high centers of the central nervous system. The use of romifidine in donkeys is not well documented and the combination of midazolam and ketamine has not been well evaluated in donkeys. The degrees of analgesia produce by romifidine in donkeys like other α-2 agonist drugs contribute to analgesia activating descending adrenergic nociceptive pathways (33). Midazolam has been demonstrated to enhance the analgesic effect of α-2 agonists (34). ketamine produces analgesic effects by antagonizing (NMDA) receptors (35).The used of two drugs (romifidine and midazolam) which proposed that the synergistic effect, romifidine which can provide analgesia effects and continues infusion of the midazolam and ketamine to increase the time of duration.

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