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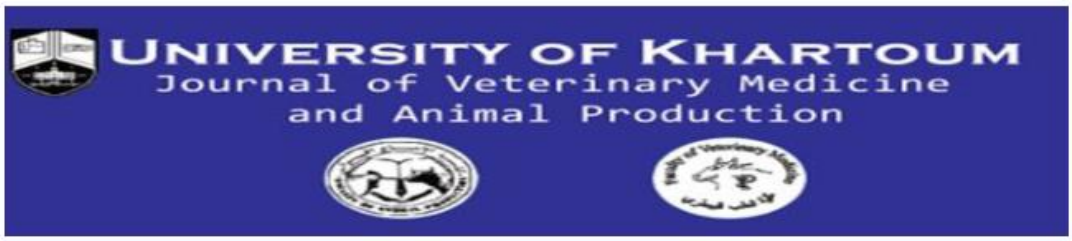

Assessment of Clinical Indices of Total Intravenous Anaesthesia Induced and Maintained Using Romifidine/Ketamine Combinations in Donkeys

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Abstract

The assessment of clinical indices following induction and maintenance of anaesthesia using two different combinations of Romifidine/Ketamine was done in donkeys. Six donkeys, 3-5 years of age with average body weight of 90±15 kg, were used in the study. Each animal was anaesthetized with one of two different protocols with two weeks' interval between each successive injection as washing out period. In the first protocol, donkeys were premedicated with 100µg/kg Romifidine (IV) and then after 10 minutes donkeys were injected with 4mg/kg ketamine intravenously for induction of anaesthesia (RK). In the second protocol, animals were treated as above and then anaesthesia was maintained immediately by intravenous infusion with ketamine 6mg/kg and romifidine100µg/kg in saline drip (RKI). Clinical indices: respiratory rate, heart rate and rectal temperature were monitored before, during and following induction of anaesthesia. Some blood biochemical parameters: urea, glucose, alanine trasaminase (ALT), and aspartate transaminase (AST) were measured before and during anaesthesia. Results obtained show that respiratory rate and rectal temperature were affected significantly ($p \leq 0.05$) as a result of using each of the two protocols. Heart rate was found to be non-significantly affected. Blood urea levels were also found to be affected significantly as a result of using the two different protocols. Glucose level, and AST and ALT activity were found to exhibit no-significant change following anaesthesia with RK or RKI. It could be concluded that the two protocols under test could be used safely in veterinary anaesthesia, although the increase in the urea level could limit the frequent or repeated usage of the two protocols on the same animal.

Key words: Donkey; Romifidine-Ketamine; TIVA, glucose, urea

Abbreviations: TIVA= total intravenous anaesthesia, K=Ketamine, R=Romifidine, I= intravenous infusion,

المستخلص

تم دراسة الآثار التخدرية الناتجة من إحداث التخدير ومواصلته باستخدام عقاري الكيتامين والروميفيدين. اجريت الدراسة على عدد ستة من الحمير من السلالات المحلية تتراوح أعمارها بين 5-3 سنوات وتبلغ أوزانها 15±90 كجم. كل حيوان تم تخديره باستخدام بروتوكولين مختلفين بفارق أسبوعين بين كل حقنين متتاليين . في البروتوكول الأول تم استخدام الرومفييدن بجرعة 100 مايكروجرام/كجم عن طرق الحقن الوريدي أتبعت بعد 10 دقائق بجرعة 4 ملجم / كجم من عقار الكيتامين عن طريق الوريد لإحداث التخدير. في البروتوكول الثاني أستخدم الروميفيدين والكيتامين كما في البروتوكول الأول واتبع ذلك بمواصلة التخدير باستخدام الكيتامين بجرعة 6 ملجم / كجم والروميفيدين بجرعة 100 مايكروجرام/كجم عن طريق التسريب الوريدي في الدرب. المؤشرات الحيوية: التنفس ودرجة الحرارة ومعدل ضربات القلب تم قياسها قبل واثناء وبعد التخدير. تم كذلك قياس بعض المعالم الحيوية في الدم : اليوريا و الجلوكوز وتركيز الاسبارتيت ترانساميناز ووالالانين ترانس امينيز . النتائج اظهرت ان هنالك فروقات معنوية حدثت في معدلات التنفس ودرجة حرارة الجسم نتيجة لاستخدام البروتوكولين. ضربات القلب اظهرت فروقات غير معنوية. حدثت زيادة معنوية في تركيز اليوريا بالدم نتيجة لاستخدام البروتوكولين. معدلات الجلوكوز والاسبارتيت ترانساميناز ووالالانين ترانس امينيز اظهرت تغيرات غير معنوية نتيجة لاستخدام البروتوكولين التخديريين. في الختام يمكن القول ان البروتوكولين التخديريين موضع الدراسة يمكن استخدامهما بامان وسلامة في هذه الفصيلة من الحيوانات الا ان زيادة تركيز اليوريا في الدم قد يكون عاملا محددا لتكرارا الاستخدام.

الكلمات المفتاحية: الحمار، الكيتامين والروميفيدين، التخديرالوريدى الكامل، الجلوكوز، اليوريا

Introduction

Reliable, efficient, safe and reversible anaesthesia necessitates the selection of appropriate agents, use of suitable techniques and precise dosing. Different methods can be used for induction of anaesthesia in donkeys, depending on the availability of drugs, size and condition of the donkey and familiarity with different protocols (Matthews and Van Dijk, 2004). In general, short-term anaesthesia in horses can be accomplished with alpha-2/ketamine combinations (Caulkett, 2007). Field anaesthesia can be maintained for up to 1 hour with a mixture of xylazine (X), ketamine (K), and guaifenesin (G) (Caulkett, 2007). The combination of guaifenesin, ketamine and α2-adrenoceptor agonists (α2-agonists: xylazine, detomidine, medetomidine, romifidine) has have been used for the prolongation of anaesthesia in horses for a long time (McCarty *et al.*, 1990, McMcurphy*et al.*, 2002, Young *et al.,* 1993).

Respiratory rate is one of the traditional vital signs that should be monitored in every patient. However, it has been described as being the neglected vital sign. As part of an initial evaluation for a patient respiratory rate provides critical information to the bedside clinician. Respiratory rate is an important indicator of wellbeing of a patient (Kelley, *et al.,* 2014).

Anaesthesia and surgery have a wide range of effects on cardiovascular system. Even in healthy patients having minor operations anaethtic agent can cause a significant cardiac depression and hemodynamic instability (Brker. ,1987).

All of the intravenous anaesthetic are detoxified in the live through liver enzymes, their detoxification may exhaust the liver. Exhaustion of the liver could be measured by measuring the level of serum liver enzymes.

In donkey, romifidine, midazolam and ketamine was used for inductionand maintenance of anaesthesia using ketamine and midazolam prepared in 500 ml normal saline was attempted in donkeys with successful results (Amin *et al.*, 2012a). Combination of ketamine with either xylazine or detomidine was

also attempted in donkeys with good results (Ghurashi*et al.*, 2016a, b).

We hypothesized that a Romifidine-Ketamine (RK) and continuous infusion with Romifidine and Ketamine combination (RKI) for maintenance of anaesthesia would provide safe and effective anaesthesia with minimal effect on cardiovascular system, liver and kidney function. Therefore, the objective of the current study was to evaluate the cardio-pulmonary and some blood biochemical effects following induction and maintenance of anaesthesia in donkeys using two combinations of Romifidine/ketamine.

Materials and methods

Place of the study: This study was carried out at the College Farm, College of Veterinary Medicine, Sudan, University of Science and Technology, Khartoum North, Hillat Kuku, Sudan.

Drugs*:* the drugs used were Ketamine Hcl 5% (Trokia pharmaceutical Ltd. Thol-282728 Gujarat, India) and Romifidine 1% (BoehringerIngleimVetmedicaGmbhBlinger 17355216 Inglheim)

Injection set*:* Disposable syringes 5, 10 and 20, and intravenous catheters (18 G) were used for intravenous injection of drugs. Normal saline drips and micro dripper 500 ml/hr was used for infusion.

Experimental animals*:* A total of six healthy donkeys of local breed, four males and two females were used in this study. Their age was between 3-5 years, with average body weight of 90±15 kg. The animals were kept in closed pens in the College farm, throughout the duration of the study. The animals were fed on green fodder, hay and supplemented with concentrates with free access to water. The animals were kept for two weeks to get acclimatized before starting experiments. Thorough clinical examination was conducted before starting experimental work, after every experiment and routinely throughout the course of the study.

Anaestheticprotocols*:*Two different anaesthetic protocols were used as follows:

1.Romifidine 1% (100µg/kg) +
Ketamine 5% (4mg/kg)

2.Romifidine 1% (100µg/kg) + Ketamine 5% (4mg/kg) + intravenous infusion with saline drip containing Romifidine 1% (100µg/kg) + Ketamine 5% (6mg/kg).

Induction of anaesthesia with ketamine was carried out 10 minutes after injection of Romifidine.

Maintenance of anaesthesia: Maintenance of anaesthesia with Romifidine/Ketamine infusion was done using saline drip with calibrated microdripper immediately and as soon as possible after induction of anaesthesia with ketamine. The drip was calibrated to come to an end at 20±2 minutes

Anaesthesia Phases and scales:

Physiological indices*:*

Respiratory rate, heart rate and rectal temperature were monitored before injection of Retomidine, 10 minutes after injection of Retomidine, immediately after induction of anaesthesia, and at 10 minutes interval until full recovery was attained following induction of anaesthesia, using standard methods (Kelly, 1984).

Blood samples collection and Biochemical analyses*:* Blood samples were collected before injection of the premedication and at 30, 60 and 90 minutes interval following the injection of the anaesthetic. Whenever blood sample was collected it is delivered immediately to the laboratory to separate plasma in eppendorf container and kept at -20°C until analysis. Urea, Glucose,

AST and ALT were measured using commercial kit (Vitro Scient-Egypt) according to colorimetric methods described by Fawcett and Scott (1960), Barham and Trinder, (1972), and Reitman and Frankel (1957).

Data analyses*:* data were expressed as mean± standard error of mean in each group. ANOVA was used to compare data for physiological parameters and blood biochemical values. The means were separated using least significant difference (LSD). A probability value of less than or equal to 0.05 ($p \leq 0.05$) were considered significant where applicable. GraphPad Prism 5.0 (GraphPad Software) was used to perform these analytical operations.

Results

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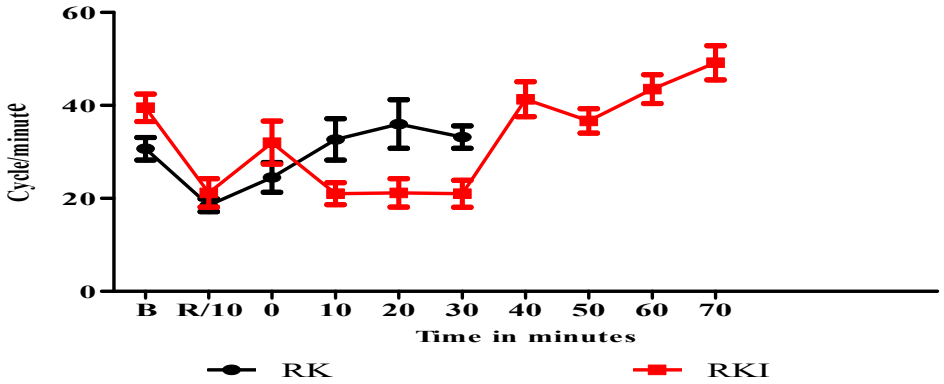
Induction of anaesthesia with RK resulted in a significant decrease ($p \leq 0.05$) in the respiratory rate 10 minutes following injection of Romifidine. The respiratory rate returned to the normal rate 10 minutes following induction of anaesthesia (Figure 1). Induction and maintenance of anaesthesia with RKI resulted in a significant decrease ($p \leq 0.05$) in the respiratory rate at 10 minutes following injection of Romifidine and at 10, 20 and 30 minutes following induction and maintenance of anaesthesia. Induction of anaesthesia with RK and induction and maintenance of anaesthesia with RKI were found to cause no-significant change in the heart rate as shown in (Figure2).



Fgure 1: Effect of induction and maintenance of anaesthesia with RK and RKI on respiratory rate

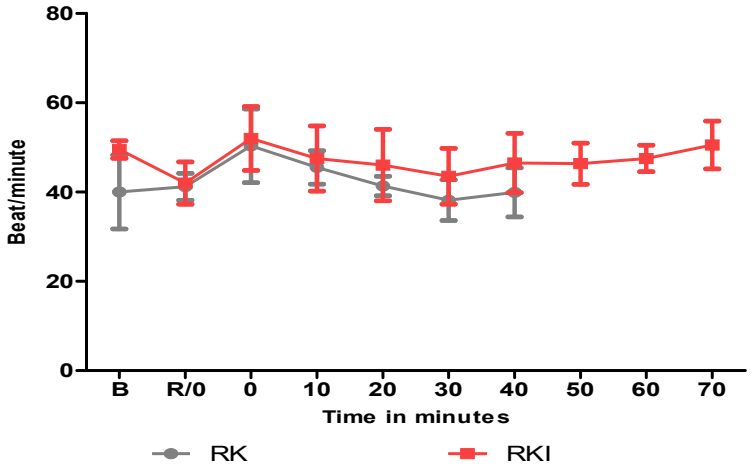


Figure 2: Effect of induction and maintenance of anaesthesia with RK or RKI on heart rate

A significant ($p \leq 0.05$) decrease in the rectal temperature was observed 10 minutes after injection of Romifidine in both protocols. Induction of anaesthesia with RK resulted in a significant drop ($p \leq 0.05$) in body temperature 10 minutes after injection of Romifidine and non-significant drop in body temperature observed during the course of anaesthesia.Induction and maintenance of anaesthesia with RKI resulted in significant decrease ($p \leq 0.05$) in rectal temperature 10 minutes after injection of Romifidine and it remained at significantly decreased ($p \leq 0.05$) level until 50 minutes following induction of anaesthesia as shown in figure 2.

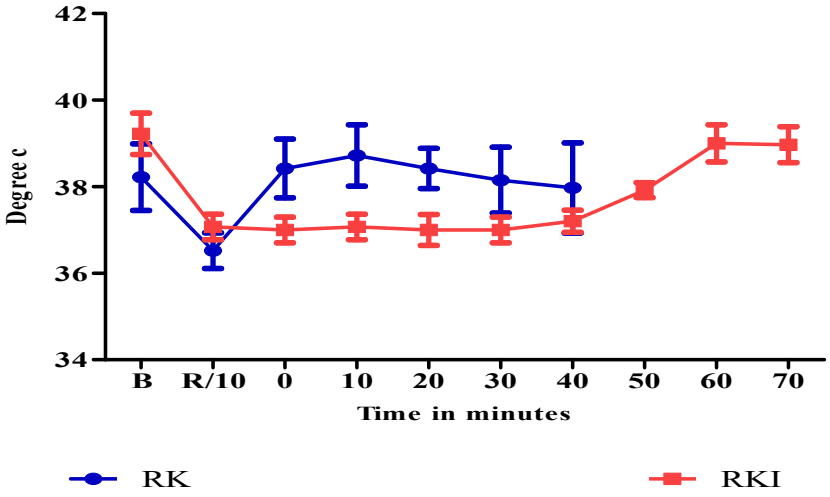


Figure 3: Effect of induction and maintenance of anaesthesia with RK and RKI on rectal temperature

Induction of anaesthesia with RK and induction and maintenance of anaesthesia with RKI resulted in significant increase($p \leq 0.05$) in urea level at 30, 60 and 90 minutes following induction of anaesthesia in the two protocols when compared to the base line values. Glucose level, and AST and

ALT activity exhibited no-significant change following induction of anaesthesia and induction and maintenance of anaesthesia with RK and RKI, respectively.

Table: Effect of induction and maintenance of anaesthesia with RKI on some blood biochemical constituents

Parameters (unit)	Protocols	Time (minutes)			
		Base	30	60	90
Urea (mmol/l)	RK	3.98±0.52a	5.46±0.57b	5.55±0.73b	5.51±0.89b
	RKI	3.49±0.77a	5.02±0.66b	5.02±0.89b	4.94±0.88b
Glucose (mmol/l)	RK	3.77±1.28a	4.47±1.73a	5.43±2.11a	5.48±2.37a
	RKI	3.20±0.97a	4.26±1.31a	5.67±1.491a	5.83±2.60a
ALT (UI)	RK	6.83±3.63 a	6.78±1.59 a	6.52±1.26 a	6.15±1.52 a
	RKI	7.90±1.34 a	7.68±0.756 a	8.35±1.46 a	9.50±2.18 a
AST (UI)	RK	81.13±5.51 a	82.99±6.23 a	80.19±8.57 a	77.40±8.83 a
	RKI	84.62±11.03 a	79.96±6.94 a	79.94±19.08 a	84.44±7.93 a

- Different letters in the same raw indicate significant difference ($p \leq 0.05$)
RK=romifidine-ketamine combination
RKI=romifidine-ketamine and intravenous infusion with romifidine and ketamine in saline drip

Discussion

Results obtained in the current study using RKI provided general anaesthesia that is considered safe with minimal changes in cardiopulmonary, liver and kidney functions.

Increase in urine production observed in the current study is in agreement with the observations of White (2006) who showed that α2-adrenoceptor agonists (xylazine-detomidine) produce bradycardia and an increase in urine production. Frequent urination was observed to occur as a result of using Romifidine alone or in combination with butorphanol in baladi goat (El-Kammar*et al.,* 2014). In donkeys romifidine at different dose levels caused increased urination (El-Maghraby*et al.,* 2005).

A reduction in respiratory rate is observed following the use of Romifidine in horses (Figueiredo*et al*, 2005), a result that is in agreement with the observed decrease in respiratory rates following injection of Romifidine in donkeys. Since Ketamine has been reported to have maintenance or stimulatory effect on respiratory system (Tokics*et al*., 1987, Morse *et al.*, 2004 and Von Ungern-Sternberg *et al.,* 2007). Therefore, the significant decrease in the respiratory rate may be due to the effect of Romifidine which was reported to cause a depressive effect on respiratory rate (Shekidef*et al*., 2007, De-Rossi. *et al*., 2009, and El-Kammar*et al*., 2014).

In the opposite direction, Romifidine was reported to cause different effects on the respiratory rate. Amin*et al.*, (2012b) reported significant increase in the respiratory rate in she donkeys as a result of using Romifidine in combination with midazolam and Ketamine. While, Taylor*,* (2001) and Kerr*et al.,* (2004) reported a non-significant effect of Romifidine on respiratory rate in horses.

Several reports indicated bradicardiogenic effect of Romifidine (Pypendop and Verstegen, 2001, Shekidef*et al*., 2007, De-Rossi*et al.,* 2009, Amin*et al*., 2012- b, and El-Kammar*et al.,* 2014). The increase in the heart rate observed in the current study

may be attributed to the excitement that might occur during induction of anaesthesia. While, the no significant drop in heart rate is partially supported by the findings of Lemke (1999), who reported bradycardia as a result of using Romifidine. Usage of high dose of Ketamine could be the factor which leads to the no significant effect on heart rate known that ketamine might have stimulatory effect on heart rate (Haskins*et al*., 1985),

The significant drop in rectal temperature following injection of Romifidine is in agreement with the findings of Lemke, (1999) who reported a hypothermic effect of Romifidine in dogs. The significant drop in rectal for 30 minutes observed in the second protocol (RKI) is in line with the findings of Amin*et al.,* (2012a) who indicated significant hypothermia in donkeys as a result of using Romifidine in combination with midazolam and ketamine.Similar results of significant decrease in body temperature in goats were reported (El-Kammar*et al.,* 2014). RK resulted in hypothermia for short time and body temperature returned to the normal values and this could be due to recovery of the animal from anaesthesia.

Both protocols caused significant increase in blood urea which observed during the whole course of anaesthesia a finding that is in line with the findings of Shekidef*et al.,* (2007) in buffalo calves. El-Maghraby*et al.,* (2005) reported that the effect of Romifidine on urea level is dose dependent, they found that injection of Romifidine at dose of 35 and 70µg/kg resulted in no significant change in urea level while the dose of 100µg/kg caused a significant increase in urea level at 60 and 90 minutes after injection of Romifidine.

The noticeable no significant increase in glucose level observed in the current study is partially in agreement with previous results that showed significant increase in glucose level following Romifidine injection (Shekidef*et al.,* 2007, Amin *et al*., 2012a, and El-Kammar*et al.,* 2014). Romifidine causes significant increase in serum glucose level as a result of using it alone (El-Maghraby*et al.,* 2005) or in combination with other drugs (Amin*et al*., 2012a).

The no significant effect of Romifidine/Ketamine on ALT and AST activity may indicate a minimum effect of the drug on the liver function and muscles myopathy. A similar observation was reported in she donkeys anaesthetized with Ketamine/Romifidine combination (Amin*et al.*, 2012a). In buffalo calves and goats significant increase in AST level was reported to occur (Shekidef*et al.,* 2007, and El-Kammar*et al.,* 2014).

Conclusion

Results obtained in the current study using RKI provided general anaesthesia that is considered safe with minimal changes in cardiopulmonary function. The quality of induction, muscle relaxation, and recovery were acceptable in donkeys. Further studies are required to evaluate effectiveness of such protocol for performing surgical operations.

Acknowledgments

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