Clinical and Renal Function Assessments of Two Total Intravenous Anesthesia Protocols in Laparoscopic Surgery

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Abstract

General anesthesia is used basically in the laparoscopic procedures in the equine. In equine, the pathological information in the urinary system is considered uncommon and very little information regarding the donkey. The aim of this study was to evaluate two protocols of total intravenous anesthesia (TIVA) by the laparoscopic surgery and body position. Ten Female donkeys were allocated randomly into two equal groups (five in each). In the first group of (DMK) was inducted by detomidine 0.02 mg /kg, midazolam, 0.1 mg / kg and ketamine 2.2 mg/kg BW, and maintenance anesthesia by detomidine 0.2 ml, midazolam 2 ml and ketamine 20 ml. The second group (DDK) was received similar drugs with replacement of midazolam by diazepam. The induction of anesthesia in the DMK protocol provided a good and general anesthesia within 12±2 minutes and caused good muscles relaxation with complete unconsciousness and complete disappearance of all reflexes in animals of this group**.** In the DDK group, the protocol provided good muscles relaxation, sedation and analgesia within 8±2 minutes shorter than DMK group. The recovery of the animals was smoothly and it ranged within 12-20 minutes in the DMK group, while it was longer in DDK animals which within 20-35 minutes. The reflexes of limbs were returned at 12±2 minutes in DMK group, while 8±3 minutes in the DDK group. The animals in DMK group showed decreasing in heart rate beats about 41.8± 1.113 during the first five minutes, while group DDK showed the heart rate beats about 36.6± 1.0294, 0.8±1.157 of treatment compared to the control group with about 46± 1.067, 40.8 ± 1.157 respectively with statistical significant differences at $P<0.05$ in 5 minutes compared with control group. The detection of renal functions of blood urea nitrogen mg/dl and creatinine mg/dl, the blood urea nitrogen show significant increase in DMK group was clear than DDK group. In conclusion, the effect of TIVA and CO_2 insufflation has significant effect in creatinine and blood urea concentration in both groups while in physiological parameter the group of DDK was more suitable than group DMK except the recovery was longer in group DDK than group DMK.

Key words: General anesthesia, renal function, laparoscopic, TIVA

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Introduction

General anesthesia technique is used in the equine species to perform laparoscopic procedures. Laparoscopy is used for applications of therapeutic, diagnostic and prognostic technique in the horse, which is usually performed on dorsal recumbency [1]. Dorsal recumbency in an anesthetized equine species and pneumoperitoneum is associated with cardiovascular, and respiratory depression [2-4]. The combined effects of intra-abdominal CO_2 gas insufflations and trendelenburg position have not been studied in horse that underwent laparoscopic surgery [5]. In the field, the short technique of injection anesthesia was used for many years. On the other hand, a TIVA is considered safe and more practical for short operation performed outside of the operating room and can be used for more techniques that are prolonged. Detomidine HCl is a potent sedative and analgesic used in veterinary practice [6]. Alpha-2-adrenorecepter agonist has high specificity and concentrations that might stimulate alpha-1-adrenorecepter [7]. The drug is metabolized in the liver, which expelled through urine and feces [8]. Benzodiazepine agonists' doses are dependently and induced the anxiolytic, muscle relaxant, anticonvulsant, sedative and hypnotic effects [9]. Midazolam is a short-acting benzodiazepine was used for induction of anesthesia [10], it is metabolized and then excreted as glucuronides into the urine [11]. Diazepam is a benzodiazepine compound widely used therapeutically [12], it has been used as tranquilizer for the cure of diseases of the central nervous system [13]. Ketamine is a phencyclidine derivative that produces a dissociative state of anesthesia [14]. The serum tests of creatinine and urea are used as indirect measurements of the glomerular filtration rate (GFR), plasma creatinine and urea are normally clarified, which reabsorbed or secreted by the proximal tubules to a minor extent, in addition to renal damage, the GFR might be reformed by changes of renal hemodynamics or extracellular dehydration [15]. However, the aim of this study was to evaluate two protocols of total intravenous anesthesia (TIVA) by the laparoscopic surgery and body position

Materials and Methods

Ten clinically healthy female donkeys weighing between 75-100kg on 12-18 months-old were used in this study. Animals were held from food for 36 hrs and water for 12 hrs before operation.

The animals were divided randomly into two equal groups: First group was administrated by detomidine, midazolam and ketamine (DMK), and second group was administrated by detomidine, diazepam and ketamine (DDK). The protocol of general anesthesia in the DMK group was administrated of detomidine in a dose of 0.02 mg/kg BW intravenously (IV) into the jugular vein as a premedication, then after five minutes, a mixture of midazolam in a dose of 0.1 mg/kg BW and ketamine in a dose of 2.2 mg/kg BW was administrated IV. Ten minutes later, an infusion of detomidine 20 µg (0.2 ml) and midazolam 10 mg (2ml) mixed with ketamine 1000 mg (20ml) in 500 ml of normal saline were administrated to maintain the anesthesia. The rate of dripping was 80 -100 drops per minute (20 drops equal to 1ml). In the DDK group, the animals received similar drugs with replacement of midazolam by diazepam 0.1 mg / kg in induction and 10 mg (2 ml) in maintaining anesthesia. The rate of dropping was 76-90 drops per minute. Detomidine, (Domosedan®) was used as a premedication drug (each ml contains 10mg detomidine; the vial contains 5 ml Vet injection, ORION pharmaceuticals, ESPOO, FINLIND). Midazolam (Midazolam®) 5 mg in 1 ml, Alsaad pharmaceuticals, Syria. Diazepam (ALSAVAL®) vial 2ml each ml contains 5 mg, Alsaad pharmaceuticals, Syria and ketamine, KANOX® each ml contains ketamine Hydrochloride equivalent to ketamine 50 mg. The vial contains 10 ml, Duopharma (M) SAN BHD, Selangor, Malaysia) was used for induction and maintain the general anesthesia.

The animal was put in dorsal position with the head and chest part of the body slightly rotated to right side. A complete laparoscopic system supplied by Karl Storz (Company Germany) is used in this study. All animals were insufflated using CO_2 gas intra peritoneal at a rate of 3.5 L/minute to obtain 10-12 mmHg intra-abdominal proper pressure for gastric operation for more than 75 minutes. Cardiopulmonary effects and rectal body temperature were recorded before giving any drugs as control data, after 5, 10 minutes and then each 10 minute till 90 minutes of the operation. Type and time of induction of all animals were

carefully observed from the moment of premedication administration until the disappearance of the reflexes that evaluated the induction, which involved the smooth, shivering or struggling movements. The induction time was also recorded and the nature of recovery was observed from the time of reappearance of the reflex until complete consciousness of smooth, staggering or difficult and standing.

Five ml of blood samples were collected via jugular vein puncturing with 23-G needle. The blood collected in the plain tubes allowed at room temperature and centrifuged to harvest the serum. Serum was stored at -20^{0}C until analysis by using diagnostic kits and spectrophotometer. The biochemical changes of this regime were evaluated by renal enzyme activities (Urea and creatinine mg/dl). Blood urea nitrogen and creatinine concentrations were estimated before the administration of the drugs. Within 30 minutes and 60 minutes of CO_2 insufflations and then 60 minutes, 24 hours and 72 hours after end of CO_2 insufflations, the blood urea nitrogen and creatinine concentrations were measured kits manufactured by AGAPPE Diagnostics Switzerland GmbH, Switzerland. Than results were expressed as M± SE. Parametric data were analyzed using two ways analysis of variance (ANOVA) continued with Least Significant Difference (LSD), and $p< 0.05$ was considered significant used Statistical Package for Social Sciences (SPSS) [16].

Results

All animals were showed signs of sedation after 3-4 minutes of administrating. This protocol cause rapid induction within 30-60 second. The induction of anesthesia in the DMK protocol provided a good and general anesthesia within 12±2 minutes and caused good muscles relaxation with complete unconsciousness and complete disappearance of all reflexes in animals of this group**.** In the DDK group, the protocol provided good muscles relaxation, sedation and analgesia within 8±2 minutes shorter than DMK group. The recovery of the animals was smoothly and it ranged within 12-20 minutes in the DMK group, while it was longer in DDK animals which within 20-35 minutes. The reflexes of limbs were returned at 12±2 minutes in DMK group, while 8±3 minutes in the DDK group. Sternal recumbence was continued for 15 minutes later in the DMK group, while 25 minutes in the DMK group (Table 1).

Table (1): The time incidence of two general anesthetic protocols

Group	Induction time second	Anesthetic time (Minutes)		Recovery time (Minutes)
		Induction	Maintenance	
DMK)	30-60	12±2	90±8	12-20
DDK	45-60	8±2	90±10	20-35

The animals in DMK group showed decreasing in heart rate beats about 41.8± 1.113 during the first five minutes, while group DDK showed the heart rate beats about 36.6± 1.0294, 0.8±1.157 of treatment compared to the control group with about 46± 1.067, 40.8 ± 1.157 respectively. The statistical analysis revealed that significant differences at the level of ($P<0.05$) in 5 minutes compared with control group. While among treated groups, the DMK was showed significant differences compared to DDK group at 50-90 minutes (Table 2).

The statistical analysis of respiratory rate showed significant differences at the ($p< 0.05$) between period 5, 10, 20, 30, 40, and 50 minutes in group DMK compared with control group, while the effect of TIVA showed less in DDK group and the significant differences at the ($p< 0.05$) between 5, 20 and 30 minutes compared with the control group. There was a significant difference sat 20, 30 and 40 minutes between the groups. The statistical analysis of core body temperature showed significant differences at the ($p < 0.05$) between control and DMK, and DDK group (Table 2).

The detection of renal functions of blood urea nitrogen mg/dl and creatinine mg/dl, the blood urea nitrogen show significant increase in DMK group was clear than DDK group. DMK group showed significant differences between control with all time while in group DDK between control and ½ hr. CO2 with other periods. The statistical analysis showed a significant increase in DMK group compared to the DDK group (Table 3). Creatinine mg / dl was decreased under basic in ½ h CO2 in both groups. In DDK group enzyme assay was appeared non-significant differences between time excepted in 1 day after anaesthesia. The DDK protocol was appeared minimal effect on creatinine enzyme activity, on the contrary from DMK protocol was causes decease in enzyme activity until 3days was increase above normal and show significant differences with all time.

Discussion

The recovery donkeys persisted quiet but they needed two attempts to stand the DMK group, while DDK group needed more than two attempts to stand. These results agreed with Matthews and Taylor [17] who revealed that the donkeys might continue in the sternal recumbence until they are relatively able to stand unassisted. These animals might need more tolerate "boost" on the tail. The reflexes of limbs were returned faster in DMK group than DDK group, these could because of the half live of midazolam is shorter than diazepam. This result is agreed with pervious reported by Plumb [18] who showed that diazepam in horses that might cause a muscle weakness and ataxia at doses enough to cause sedation, dose larger than 0.2 mg/kg might induce recumbency as an effect of its muscle relaxant properties and general CNS depressant effects.

The differences between both groups in heart rate beats might be due to the manipulation during gastrostomy and injection of the diazepam was little effect on heart rate than midazolam duo to midazolam is rapidly metabolized. The imidazole ring is oxidized firstlyinto the livermore quickly than the rate of oxidation of the methylene group of the diazepam ring of other benzodiazepines [11]. Serum half-live (approximated) informed for diazepam and metabolized in a horse is 7-22 hours [18]. The decreasing of heart rate beats after injection of detomidine in this study was agreed with England and Clarke [19] who revealed that α 2-adrenoceptor agonists might cause rapid drop in heart rate initially within the first minute. The rise in heart rate beats during CO_2 pneumoperitoneum in laparoscopic surgery because possibility of the CO_2that might induce hypercarbia. An alteration on blood gases and cardiac arrhythmias with prolonged procedures and CO_2preservationarepossible caused tachycardia and acidosis [20]. On the other hand, the heart rate beats was increased due to the ketamine effect on cardiovascular stimulating properties [21].

The respiratory rate was decreased during the first five minutes duo to the result of airways relaxation by presynaptic inhibition of acetylcholine release from cholinergic nerves in airways, which was arbitrated by stimulation of α 2- adrenoceptors [22]. Injection of benzodiazepines also might lead to respiratory depression [23]. Increasing in the respiratory rate may be attributed to the excitement of the animal during IV injection of midazolam or

diazepam - ketamine due to excitement phases of stage 1 and stage 2 of general anesthesia. The increasing in respiratory rate during CO_2 insufflations in this study agreed with Motew and Ivankovich [24] who revealed that the respiratory system experiences a marked decrease in lung capacities because of the cranial shift of abdominal viscera, and the effect of CO_2 pressure on the diaphragm which increased ventilation/perfusion mismatching, atelectasis and decreased pulmonary compliance.

The results of temperature agreed with the other researcher who found that the effect of α-2 adrenoceptors drugs which causes depression of hypothalamic thermoregulatory center [19, 25, 26] decreased in body temperature during general anesthesia was due to reduced the basal metabolic rate and muscle activity [6]. Ketamine and other dissociative anesthetics which cause hypothermia by emancipating monoamines responsible for centrally mediated hypothermia by inhibiting endogenous release of norepinephrine [27].

The renal effects are mild to negligible once the intra-abdominal pressure is less than 10 mmHg, but as intra-abdominal pressure extents and surpasses 15 mmHg, there's a pressure-dependent reduction in the glomerular filtration rate, creatinine clearance, sodium excretion, and urinary productivity. Oliguria is often seen otherwise expected with increases in intra-abdominal pressure during laparoscopy and really should be defined as a normal physiologic response. Intra-abdominal pressure increases causes compressive effects on the renal vasculature, the renal parenchyma, and will decrease current renal blood circulation, cortical and medullary perfusion, and renal venous outflow [28, 29]. In conclusion, the effect of TIVA and CO_2 insufflation has significant effect in creatinine and blood urea concentration in both groups while in physiological parameter the group of DDK was more suitable than group DMK except the recovery was longer in group DDK than group DMK.

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Table 2: Shows the effect of TIVA by DMK or DDK and CO_2insufflations on heart rats (beat/min), Respiratory rate (breath/minute) and rectal body temperature °C

GROUP	Time of experiment Minutes										
	0	5	10	20	30	40	50	60	70	80	90
DMK (HR)	46.2±1.067 a	41.8± 1.113 b	46.8±0.734 a	45.8±0.969 a	45.2±1.200 a	48.4±2.580 a	51±1.264 aA	50±1.303 aA	50±1.303 aA	51±1.264 aA	49±0.894 a
DDK (HR)	40.8±1.157 a	36.6±1.029 b	44±0.316 a	44±0.547 a	42±0.894 a	42.2± 0.489 a	42.4±0.979 a B	43.4±0.979 a B	43.4±0.400 a B	44±0.632 a B	44.8±0.374 a
DMK (RR)	18.4±0.979 d	16.4±1.939 e	19.4±1.326 d	27.2±1.392 aA	24±1.264 b A	22±0.632 aA	20±0.632 c	19.4±0.400 D	19.8±0.663 d	19.4±0.979 d	19.8±0.200 d
DDK (RR)	18.4±0.979 c	15.6±1.166 d	18.4±0.979 d	23.2±1.019 d B	20±0.632 b B	17.6±0.979 c B	19±1.341 c	17±0.774 C	17.4±0.400 c	17.4±0.748 c	18.4±0.400 c
DMK (BT)	38.1±0.234 a	37.8±0.269 ab	37.6±0.240 ab	37.4±0.249 ab	37.3±0.249 ab	37±0.199 ab	36.8±0.184 b	36.6±0.126 B	36.6±0.158 b	36.6±0.159 b	36.9±0.193 b
DDK (BT)	38.3±0.122 a	38±0.174 ab	37.8±0.174 b	37.6±0.183 bc	37.5±0.156 bc	37.2±0.141 bc	36.8±0.169 c	36.6±0.116 C	36.6±0.140 c	36.7±0.092 c	37±0.172 c

Heart rats (HR), Respiratory rate (RR), Body temperature (BT), Small different letters denoted that significant differences between period ($p<0.05$) Capital different letters denoted that significant differences between groups ($p<0.05$).Small different letters denoted that significant differences between period at ($p<0.05$). Capital different letters denoted that significant differences between groups ($p<0.05$)

Table 3: The effect of TIVA by DMK or DDK and CO_2insufflation on serum urea and creatinine (blood urea mg/dl and creatininemg/dl concentration)

	Control	½h Co2	1hr CO_2	1hr after end of CO_2	1 day	3 days
DMK Blood Urea	54.68±5.611 d	60.34±3.705 b	64.12±1.420 aB	62±2.407 abB	58.88±4.049 cB	57.14±4.422 cB
DDK Blood Urea	58.06±4.048 a	58.3±2.948 a	53.02±3.527 bA	54.5±4.621 bA	50.42±3.558 cA	46.32±5.154 bA
DMK Creatinine	0.62 ±0.219 b	0.43±0.119 c	0.45±0.061 cB	0.33±0.065 dB	0.54±0.037 c	0.78±0.055 a
DDK Creatinine	0.88 ±0.176 a	0.68 ±0.249 b	0.81±0.147 aA	0.83±0.230 aA	0.70±0.160 b	0.82±0.054 a

Small different letters denoted that significant differences between period at ($p<0.05$). Capital different letters denoted that significant differences between groups ($p<0.05$)