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ORİJİNAL MAKALE

Effects of Xylazine-Diazepam-Ketamine and Xylazine-Tiletamine-Zolazepam Anesthesia on Some Coagulation Parameters in Horses

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Summary: *Xylazine-diazepam-ketamine (XDK) and xylazine-tiletamine-zolazepam (XTZ) have been always used for induction of anesthesia. There is no report regarding the effects of these anesthetics on the activated partial thromboplastin time (APTT), prothrombin time (PT) and platelet count (PLT) in horse. Therefore, this study has been conducted to search for the anesthetic combination less affecting the coagulation parameters in horses. Six healthy, mixed breed horses received XDK and XTZ anesthetic combinations at two weeks interval. Blood samples were collected before (baseline) and at 10, 30, 60 and 90 min after anesthesia and APTT, PT and PLT were measured. Although it was observed fluctuations in PT and APTT in both groups, it always remained within normal reference values of horse. In the XTZ group PLT decreased at 10 min, and increased at 60 min. On the other hand, PLT increased only at 10 min in the XDK group. There are no significant differences in PT, APTT and PLT values between groups. In conclusion, both anesthetics administration caused a fluctuation in the coagulation parameters. The small changes in these parameters are probably not clinically relevant, therefore these combinations can be used safely even in horses with coagulation disorders.*

Key words: Xylazine, ketamine, diazepam, tiletamine, zolazepam, prothrombin time, activated partial thromboplastin time, horse

Ksilazin-Diazepam-Ketamin ve Ksilazin-Tiletamin-Zolazepam Anestezisinin Atlarda Bazı Koagülasyon Parametrelerine Etkisi

Özet: *Ksilazin-diazepam-ketamin (XDK) ve ksilazin-tiletamin-zolazepam (XTZ) kombinasyonları atların anestezi indüksiyonlarında yaygın bir şekilde kullanılmaktadır. Bu anestezik kombinasyonların atlardaki protrombin zamanı (PT), aktive edilmiş parsiyel tromboplastin zamanı (APTT) ve trombosit sayısı üzerindeki etkilerini araştıran herhangi bir çalışmaya rastlanamamıştır. Bunun için bu çalışmada, atlardaki koagulasyon parametreleri üzerinde XDK ve XTZ anestezik kombinasyonlardan hangisinin daha az etkili olduğunun araştırılması amaçlandı. Altı sağlıklı ata önce XDK, iki hafta sonra da XTZ kombinasyonu uygulandı. Anestezi öncesi ve anestezinin 10, 30, 60 ve 90. dakikalarında toplanan kan örneklerinde PT, APTT ve trombosit sayıları tespit edildi. PT ve APTT değerlerinde her iki grupta dalgalanmalar görülse de bunların atlar için normal referans değerler içinde kaldığı gözlendi. XTZ grubundaki trombosit sayısının 10. dakikada azaldıktan sonra 60. dakikada arttığı görüldü. XDK grubundaki trombosit sayısının ise sadece 10. dakikada azaldığı belirlendi. XDK ve XTZ grupları karşılaştırıldığında PT, APTT ve trombosit sayıları arasında fark olmadığı tespit edildi. Sonuç olarak, her iki anestezik kombinasyon koagulasyon parametrelerinde dalgalanmalara neden olsa da, bunun hemostazisi önemli bir şekilde etkilemediği görüldü. Bu anestezik kombinasyonların PT, APTT ve trombosit sayısı üzerindeki etkilerin klinik olarak önemli olmadığı, bundan dolayı koagülasyon bozukluğu olan atlarda güvenle kullanılabileceği sonucuna varıldı.*

Anahtar kelimeler: Ksilazin, ketamin, diazepam, tiletamine, zolazepam, prothrombin zamanı, aktive edilmiş parsiyel tromboplastin zamanı, at

INTRODUCTION

Adequate hemostasis is essential during surgery, and therefore the effects of drugs used for general anesthesia on hemostasis and fibrinolysis are important clinical issues. An ideal anesthetic should not interfere with the coagulation process (1). The most common equine emergency case presented to the anesthetist is that of colic. Disseminated intravascular coagulation (DIC) is a common and potentially lethal complication of colic in horse. As many as 44 % of horses with severe colic experience DIC (2, 3). Colic results in widespread activation of the coagulation cascade, systemic generation of thrombin and consumption of coagulation factors (4). Thus, APTT and PT prolong and thrombocytopenia develops in horses with colic

(5). Minimum laboratory data needed to evaluate hemostasis in horse are PT, APTT, PLT and plasmafibrinogen. Primary hemostasis can be evaluated by determination of platelet numbers. Secondary hemostasis can be evaluated by APTT, PT and fibrinogen quantification. APTT screens the function of the intrinsic and common pathway abnormalities. Prolongation of APTT is caused by von Willebrand's disease, deficiencies of factors including F VIII (haemophilia A), F IX (haemophilia B), F XI, F XII and the presence of circulating anticoagulants (6). The APTT test is the most commonly used coagulation assay in monitoring heparin effects in patients (7). PT evaluates extrinsic and common coagulation pathway abnormalities. It may be prolonged in patient with DIC, deficiencies of factors including F II, F III, F V, F VII, F X, vitamin K or failure of the liver to produce those factors (6). Some anesthetics may prolong or shorten APTT and PT on those patients with coagulopathies under surgical interventions. These cases must be approached with caution not to aggravate the already altered coagulation parameters (8).

In the horse, XDK and XTZ anesthetic combinations have been always used for induction of anesthesia (9). Xylazine is a typical α_2 adrenoceptor agonist and exerts its effects accordingly (9). Ketamine, dissociative anesthetic, acts as a sympathetic stimulant and counteracts some of the vagotonic effects of the α_2 agonist, while the α_2-agonist drugs minimize some of the muscle hypertonicity associated with the use of ketamine in horses (10). Diazepam, benzodiazepines analgesic, increases the length of action of other anesthetics agent and the drug is particularly useful prior to ketamine anesthesia (9). Tiletamine-zolazepam (TZ) chemically, the preparation is a combination of equal parts of tiletamine HCl, and zolazepam HCl (11). Tiletamine is a dissociative agent closely related to ketamine. Zolazepam, a minor benzodiazepine tranquilizer is similar to diazepam, acting centrally to induce muscle relaxation (12). We have found no reports regarding the effects of these anesthetics on the APTT, PT and PLT in horse. Therefore, this study was conducted to determine whether the injectable anesthetics could be used in horse undergoing surgery and to search the most suitable anesthetic combination in respect to the coagulation parameters

MATERIALS AND METHODS

Six healthy, mixed breed horses of both sexes, ranging in bodyweight from 200 to 320 kg, were used in this study. Horses received XDK and XTZ anesthetic drug combinations at two weeks interval. In the XDK group, general anesthesia was induced by injecting 1.1 mg kg^{-1} xylazine (Rompun®, Bayer, Turkey), and after 5 min 2.2 mg kg^{-1} ketamine HCl (Alfamine®, Egevet, Turkey) and 0.05 mg kg^{-1} diazepam (Diazem®, Deva, Turkey) intravenously. In the XTZ group, 5 min after premedication with xylazine (1.1 mg kg^{-1}), anesthesia was induced with 1.65 mg kg^{-1} tiletamine-zolazepam (Zoletil 50®, Virbac, France).

Blood samples were collected by jugular venipuncture before (baseline) and at 10, 30, 60 and 90 min after anesthesia. APTT and PT were measured in citrated plasma samples by using an automated coagulation analyzer (BTC Coagulation Timer, Dade Behring, Germany). PLT was determined immediately in EDTA-anticoagulated blood by using a hematology analyzer (Coulter MD 18, Beckman, USA). Data were analyzed using General Linear Model (GLM) for repeated measures followed by Wilcoxon Signed Rank Test on SPSS software 10.1.0.

RESULTS

The mean values of PT, APTT and PLT during anesthesia in the XDK and the XTZ groups were shown in Table 1.

Prothrombin time significantly shortened ($P<0.05$) at 30 min in the XTZ group, while no significant changes observed in the XDK group. XDK anesthetic administration caused statistically significant prolongation for APTT only at 10 min ($P<0.05$) compared to baseline value. XTZ combination administration had no significant effect on APTT during anesthesia. Platelet count increased significantly at 10 min in the XDK group ($P<0.05$). In the XTZ group, PLT decreased significantly at 10 min ($P<0.05$), and increased at 60 min ($P<0.05$). Comparison of XDK to XTZ on the effects of PT, APTT and PLT showed no significant differences at all time intervals. The changes in all parameters remained within the normal references values of horses.

Table 1. The values of PT, APTT and PLT during Xylazine-Diazepam-Ketamine (XDK) and Xylazine-Tiletamine-Zolazepam (XTZ) anaesthesia (mean± SD) (n=6).

Parameters	Groups	Time (min)				
		Baseline	10	30	60	90
PT	XDK	14.8±1.9 x	15.0±1.4	14.3±2.2	15.0±1.5	14.2±1.2
(sec)	XTZ	13.7±0.3 a,y	13.5±0.5a	12.6±0.9b	13.5±0.6a	13.4±0.6a
APTT	XDK	36.1±2.7a	39.3±3.5b	38.0±4.8ab	39.1±2.3ab	38.3±4.2ab
(sec)	XTZ	36.2±6.1	37.7±5.2	37.9±7.1	37.3±7.5	37.4±6.4
PLT	XDK	191±18.1a	202.5±14.7b	198.5±16ab	193.3±17.2ab	192.5±16ab
(x 10^3/µl)	XTZ	193±8.1ac	186±11.2b	190.8±14.2ab	201.8±14.7c	192.5±12a

Different superscripts within the row (a,b) and column (x,y) indicate significant differences ($P<0.05$).
PT: Prothrombin Time; APTT: Activated Partial Thromboplastin Time; PLT: Platelet count

DISCUSSION

Blood coagulation can be activated or suppressed in different ways. There are several reasons for the development of coagulopathies such as numerous metabolic, cardiovascular and respiratory disorders, endotoxaemia, drugs, cytokines, ions, ect. (13). Some preanesthetics such as xylazine depress cardiovascular and respiratory activity and produces hypotension, hypoxia and acidosis (14). On the other hand, other anesthetics such as ketamine and tiletamine have hypertensive effects (9). Hypotension decreases platelet aggregation without any influence on other coagulation factors, thus protecting the coagulation system from consumptive coagulopathy (15). However, hypertension promotes platelet activation and aggregation by increasing endogenous production of catecholamines (16). Hypothermia accompanying all anesthesia types markedly suppresses blood coagulation (17). Anesthetics have been demonstrated to have an effect on the aggregation response of platelets. Anesthetics have a direct effect on the platelet membrane. The concentration at which these anesthetics mediate a platelet inhibitory effect is an order of magnitude greater than that considered to have potentially lethal effects in vivo (18).

Primary hemostasis can be evaluated by determination of platelet numbers. Secondary hemostasis can be evaluated by APTT for intrinsic and common pathway abnormalities, fibrinogen quantification for common pathway abnormalitie, and PT for extrinsic and common pathway abnormalities (6). The actual effects of xylazine, diazepam, ketamine and tiletamine-zolazepam alone on APTT and PT are not known. Stringer and Seligmann. (19) reported that slight prolongation of APTT was observed in the xylazine-ketamin administrated rats and the reason for the prolongation could not be explained. Similarly, we observed a prolongation of APTT at 10 min in the XDK group. The fluctuations in APTT and PT during anesthesia induced by XDK and XTZ might be resulted from changes in blood pressure, body temperature, respiratory rate, acidosis and stress-induced catecholamine release, as mentioned above. APTT and PT are considered to be prolonged if their time is more than 4 seconds (20). In the present study, PT and APTT were not prolonged or shortened more than 4 second at any times compared to the baseline in both groups. Although some of these changes were statistically significant, the altered coagulation parameters always remained within normal reference values of horses.

In the current study, PLT increased at 10 min in the XDK group. On the other hand, XTZ anesthesia had biphasic effect on PLT (Table 1). The changes in PLT probably resulted from different haemodynamic effects of these anesthetics. Rapidly mobilizable splenic pools of platelets are present in humans and animals. A transient increase in platelet numbers in blood occurs after epinephrine secretion. The increase in platelet counts results from the release of platelets from the spleen, thereafter it returns to normal level within 30 minutes (21). Xylazine is believed to induce sedation by stimulating α-$_2$ receptors, thereby decreasing norepinephrine release (22). A previous study reported that xylazine administration reduced PLT in sheep (23). However, in the current study, PLT significantly increased at 10 min in the XDK group. The reason of this result might be that

symphatomimetic effect of ketamin dominated the parasymphatomimetic effect of xylazine, as reported by Muir et al. (24). In the XTZ group, the significant decrease at 10 min and the increase at 60 min in PLT presumably was a result of xylazine's parasempatomimetic effect and biphasic hemodinamic effects of tiletamine-zolazepam. Biphasic hemodynamic response to TZ has also been reported in calves (25). The response was characterized by an initial decrease followed by a return to baseline, with subsequent increase above baseline for remainder of the experiments (26). Hence, these changes in PLT may attributable to fluid exchange between intravascular and extravascular space for balancing the arterial pressure changes during anesthesia as reported by Muir et al (24).

In summary, XDK and XTZ anesthetics combinations did not interfere with hemostasis importantly. The small changes in these parameters are probably not clinically relevant, therefore these combinations can be used safely even in horses with coagulation disorders.

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