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Effects of Diazepam/Propofol and Diazepam/Remifentanil Induction Protocols on the Coagulation in Dogs

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Abstract

Studying the effect of general anaesthesia on blood parameters is extremely important both in terms of patient safety and determining protocol suitability for the patient. There is no study on the assessment of the effects of Diazepam/Propofol and Diazepam/Remifentanil combination administered to dogs on clotting time, thrombin time (TT), prothrombin time (PT), active partial thromboplastin time (aPTT) and buccal mucosa bleeding time (BMBT). The purpose of the study presented is to investigate the effects of Diazepam/Propofol and Diazepam/Remifentanil combinations on coagulation parameters in dogs aged 5 years and older, requiring surgery for various reasons. Prior to anaesthesia (T0), it was found that there was no difference between the two groups in terms of PT, TT, aPTT and BMBT (p=0.426 p=0.091, p=0.166, p=0.686, p=0.209, respectively). Following anaesthesia (T1), it was found that the buccal mucosal bleeding time in dogs in the Diazepam/Remifentanil group had a tendency to be shorter (p=0.084) than those in the Diazepam/Propofol group. Also, PT in the Diazepam/Remifentanil group was longer (p=0.031) compared to the Diazepam/Propofol group. No significant difference was found between the groups with respect to clotting time, TT or aPTT (p=0.191, p=0.467, p=0.972). While it is stated that neuroleptanalgesia produces reliable anaesthesia induction in unwell patients, based on the data obtained at the end of the study, it was determined that Diazepam/Propofol combination is more reliable in the anaesthesia of patients requiring surgical intervention.

Keywords: Coagulation, diazepam, dog, remifentanil, propofol

Introduction

Hemostasis is a complex process arising as a result of the dynamic relationships between the circulatory system, thrombocytes and coagulation proteins (Chohan et al., 2011; Kamal and Kamal, 2008). The hemostatic process consists of three major phases. These are: vasoconstriction, primary hemostasis including platelet formation and secondary hemostasis comprising coagulation and fibrinolysis (Forsythe and Willis, 1989; Kamal and Kamal, 2008).

Bleeding related disorders occur in relation to vascular integrity, thrombocyte function, thrombocytopenia and von Willebrand disease. These disorders emerge with findings such as petechiae, surgical bleeding, haematomas and recurrent bleeding following formation of the first blood clot (Forsythe and Willis, 1989; Smith et al., 2005).

Thrombocyte count, clotting time, prothrombin time (PT), thrombin time (TT), active partial thromboplastin time (aPTT) and buccal mucosa bleeding time (BMBT) are the most frequently used parameters in determining coagulation disorders (Forsythe and Willis, 1989; Ogurtan et al., 2002; Smith et al., 2005).

Prothrombin time is one of the extrinsic blood coagulation tests and is used to assess extrinsic factor VII and III (Chohan

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et al., 2011; Mischke, 2011; Smith et al., 2005) PT may be prolonged in extensive intravascular coagulation, hepatic diseases or patients with Vitamin (Vit) K deficiency (Ogurtan et al., 2002).

Thrombin time is used to evaluate the conversion of fibrinogen to fibrin. Prolongation of thrombin time indicates either fibrinogen deficiency or thrombin inhibition (Smith et al., 2005).

Active partial thromboplastin time is used in the assessment of intrinsic factor XII, XI, IX and VIII. In the event of any one of these factors being less than 35% of the normal value, the aPTT will lengthen and clinical bleeding problems may be encountered. This parameter is not affected by thrombocyte count deficiency (Smith et al., 2005).

Buccal mucosa bleeding time is the best assessment method for thrombocyte function and clot formation (Chohan et al., 2011; Fresno et al., 2005). It includes the time from the incision to the first moment the bleeding stops. In healthy dogs, normal BMBT is 1.7-4.2 minutes (Forsythe and Willis, 1989; Jandrey 2012; Smith et al., 2005).

In dogs, hepatic diseases in particular affect the coagulation mechanism and cause prolongation of aPTT and PT. Normal aPTT is 8.4-14.8 seconds and PT is 6.4-8.2 seconds in dogs (Chohan et al., 2011; Ogurtan et al., 2002).

Studying the effect of general anaesthesia on blood parameters is extremely important both in terms of patient safety and determining protocol suitability for the patient (Arca and Sarıtaş, 2017; Binici et al., 2015).

Diazepam is a tranquilizer belonging to the benzodiazepine group of drugs and has no suppressive effect on heart rate, myocardial contractility or arterial blood pressure. It possesses muscle relaxant and vasodilatation producing properties. When used in combination with opioids, it produces safe sedation, particularly in elderly dogs (Guzel et al., 2018; Kürüm et al., 2013).

Remifentanil is an ultra-short-acting synthetic μ opiod agonist (Gimenes et al., 2011). In dogs, it causes a decrease in heart rate and cardiac output, bradycardia and hypotension. However, the fact that it enables rapid control of anaesthesia depth and is not dependent on hepatic metabolism or renal excretion for drug clearance is considered to be advantageous (Beier et al., 2015; Gimenes et al., 2011; Murrell et al., 2005; Pei et al., 2014). Despite being used extensively in human medicine, there are few studies on its clinical use in dogs (Beier et al., 2015; Lamont and Mathews, 2007; Pei et al., 2014).

Propofol is a short-acting anaesthetic belonging to the alkyl phenol group frequently used in Veterinary Medicine. It provides rapid induction and recovery and repeated administration causes no build-up in the body. However, in the case of high doses or rapid injection, it produces apnoea and significant hypotension (Campbell, 2005; Güzel et al., 2013; Ogurtan et al., 2002).

There is no study on the assessment of the effects of Diazepam/Propofol and Diazepam/Remifentanil combination administered to dogs on clotting time, TT, PT, aPTT and BMBT.

The purpose of the study presented is to investigate the effects of Diazepam/Propofol and Diazepam/Remifentanil combinations on coagulation parameters in dogs aged 5 years and older, requiring surgery for various reasons.

Materials and Methods

The study was conducted in accordance with the ethical principles approved by Istanbul University Animal Experiments Local Ethics Committee (26.04.2018/2018/38).

The study material comprised of 16 dogs aged 5 years and above, presented to the Istanbul University Faculty of Veterinary Medicine Surgery Department and requiring surgery for various reasons. Differences in breed and gender were not taken into account. In terms of anaesthesia risk, cases in the ASA 1 and 2 status were included in the study.

In the pre-operative period, routine physical examination was performed in all cases and haemogram (Erythrocyte-RBC, Haemoglobin-HGB, Hematocrit-HCT, Leucocyte- WBC) and blood biochemical results (Aspartate-aminotransferase-AST, Alanine-aminotransferase-ALT, glucose, urea, creatinine and total protein) were evaluated.

In all cases, food intake was stopped 12 h before and water intake was stopped 1 h before anaesthesia induction. Intravenous injections were administered to the dogs via a 22-gauge cannula placed into the cephalic antebrachial vein. Blood samples for parameter analysis for the study were obtained from the cephalic antebrachial vein in the opposite leg.

Two separate anaesthesia groups were formed, each containing 8 dogs (n=8). Dogs were selected randomly for the groups.

Group I was determined as the Diazepam/Propofol (DP) group (Diazem 10 mg, N05BA01 Deva Holding, Kocaeli/Turkey; Propofol 1%, 10 g, 20 mL, N01AX10, Fresenius Kabi Ltd, Italy). The dogs in this group were administered intravenous (IV) diazepam at a dose of 0.5 mg/kg for premedication. For induction, propofol was given at a dose of 6 mg/kg IV, 5 min after diazepam administration.

Group II was determined as the Diazepam/Remifentanil (DR) group (Diazem 10 mg, N05BA01 Deva Holding, Kocaeli/Turkey; Remifentanil, Ultiva 1 mg, N01AH06, GlaxoSmithKline plc., Italy). Again, diazepam was administered to this group at a dose of 0.5 mg/kg IV. Remifentanil was given 5 min later at a dose of 10 μg/kg via slow IV injection.

For the analysis of the aPTT, PT, and TT parameters, two sodium citrate tubes were each filled with 2 ml of blood collected from all of the dogs (n=16) before anaesthesia. This measurement time was determined as T_0.

In order to establish buccal mucosa bleeding times at the same measurement time (T_0), the right or left buccal mucosae of all dogs were punctured using a penetration device (Contour plus, Bayer, Germany) and measured with the aid of a chronometer and blotting paper. For the purpose of determining simultaneous clotting time, blood was collected into 2 capillary tubes and clotting times were observed starting from 90 sec and checking at 30 sec intervals.

Following collection of blood samples, all cases were intubated using endotracheal intubation tubes of suitable sizes. General anaesthesia was induced with 4% isoflurane and later maintained at 2% concentration.

Fifteen minutes after anaesthesia was identified as measurement time T_1. At this measurement time, all the procedures performed at T_0 were repeated before the surgical incision was made.

Blood samples were taken from the cephalic antebrachial vein of the dogs into the EDTA coated tubes and carried out at the İstanbul University, Faculty of Veterinary Medicine, Department of Physiology Laboratory. The blood samples were analysed using cell counter (Abacus Junior Vet, Austria©).

Statistical analysis

Firstly, the data was examined in terms of normal distribution in order to determine whether or not there was any difference between the effects of the anaesthetics on coagulation parameters. The difference between those demonstrating normal distribution was analysed using the independent T test. The Levene test was used to determine whether or not they exhibited normal distribution. In the comparison of those not displaying normal distribution, the non-parametric Mann Whitney U test was used. The presence of any differences between mean values measured before and after anaesthesia was analysed using the paired samples T test. All statements of significance were based on $p<0.05$ and tendencies were indicated if the P value was between 0.05 and 0.91. Statistical analysis was performed using The Statistical Package for the Social Sciences (SPSS) version 21 for Windows (IBM Corp., Armonk, NY, USA).

Results

The effects of the anaesthetics used in this study on coagulation parameters are shown in Table 1. Prior to anaesthesia (T_0), it was found that there was no difference between the two groups in terms of PT, TT, aPTT and BMBT (p=0.426 p=0,091, p=0.166, p=0.686, p=0.209, respectively).

Following anaesthesia (T_1), it was found that the buccal mucosal bleeding time in dogs in the D/R group had a tendency to be shorter (p=0.084) than those in the D/P group. Also, PT

Table 1. Differences between Diazepam/Propofol (DP) and Diazepam/Remifentanil (DR) groups regarding coagulation parameters

Before anesthesia	Buccal Mucosa Bleeding Time (second)	Clotting Time (second)	Prothrombin time (second)	APTT (second)	Thrombin time (second)
DP Group	22.0±5.04	258.7±41.25	13.1±0.56	111.1±23.59	15.3±0.80
DR Group	18.0 ±1.75	389.0±55.32	30.8±11.53	126.8±29.1	19.9±3.25
p-value	0.426	0.091	0.166	0.686	0.209
After anesthesia					
DP Group	22.7±4.93	270.0±55.83	12.7±0.49	107.2±24.31	19.9±5.39
DR Group	13.4±2.29	356.0±34.45	14.3±0.42	89.9±3.49	20.1±4.52
p-value	0.084	0.191	0.031	0.467	0.972

APTT: Active partial prothrombin time

Table 2. Changes observed in the coagulation parameters before and after anaesthesia in the group given Diazepam/Propofol combination

	Before anesthesia	After anesthesia	p-value
Buccal Mucosa Bleeding Time (second)	22.0±5.04	22.7±4.93	0.890
Clotting Time (second)	258.7±41.25	270.0±55.83	0.836
Prothrombin Time (second)	13.1±0.56	12.7±0,49	0.563
APTT (second)	111.1±23.69	107.2±24.31	0.341
Thrombin Time (Sn)	15.3±0.80	19.9±5.39	0.437

APTT: Active partial prothrombin time

Table 3. Changes observed in the coagulation parameters before and after anaesthesia in the group given Diazepam/Remifentanil combination

	Before anesthesia	After anesthesia	p-value
Buccal Mucosa Bleeding Time (second)	18.0±1.75	13.4±2.29	0.048
Clotting Time (second)	389.0±55.3	356.0±34.4	0.504
Prothrombin Time (second)	30.8±1.81	14.3±0.42	0.183
APTT (second)	126.8±29.17	89.9±3.49	0.262
Thrombin time (second)	19.9±10.2	20.1±14.3	0.974

APTT: Active partial prothrombin time

in the D/R group was longer (p=0.031) compared to the D/P group. No significant difference was found between the groups with respect to clotting time, TT or aPTT (p=0.191, p=0.467, p=0.972).

Data obtained for pre-anaesthesia (T_0) and post-anaesthesia (T_1) comparison is shown in Table 2 and Table 3. No significant difference was found between the pre-anaesthesia and post-anaesthesia clotting times, PT, TT, aPTT and BMBT in dogs in the D/P group (p=0.890, p=0.836, p=0.563, p=0.341, p=0.437, respectively).

In dogs in the D/R group, however, BMBT was found to be shorter following anaesthesia compared to before anaesthesia (p=0.048). On the other hand, no significant difference was seen between T_0 and T_1 with respect to clotting time, PT, TT or aPTT (p=0.504, p=0.183, p=0.262, p=0.974, respectively).

Discussion

In surgical interventions it is extremely important to control the bleeding at the start of the incision and provide hemostasis (Charlesworth et al., 2012). Anaesthetic drugs may alter the diameters of arterioles and venules and the reaction of these structures to stress. During general anaesthesia, vasodilatation occurs, blood flow decreases and the rate of thrombosis formation increases (Binici et al., 2015).

Diazepam, used extensively in clinical Veterinary Medicine, has no suppressive effect on the cardiovascular system (Kürüm et al., 2013). However, it produces vasodilatation in blood vessels in connection with its muscle relaxant effect (Guzel and McKinstry, 2017; Guzel et al., 2018). Propofol, a general anaesthetic used regularly in Veterinary Medicine leads to a significant degree of hypotension in the event of high doses or rapid intravenous injection (Campbell, 2005; Güzel et al., 2013; Ogurtan et al., 2002). In the first study, group of D/P combination, no suppressive effect was observed to occur on parameters investigated in terms of coagulation. This was because no statistically significant difference was determined between investigations performed before anaesthesia (T_0) and after the anaesthesia protocol administration (T_1).

The endotracheal intubation procedure triggers the cough reflex in patients. This stimulation produces an increase in the sympathetic tone and leads to tachycardia and hypertension (Güzel et al., 2013). In neuroleptanalgesia performed with a tranquilizer and opioid combination, haemodynamic changes caused by endotracheal intubation occur to a lesser degree. In this study, in the anaesthesia administration with D/R, no significant difference was observed between pre-anaesthesia and post-anaesthesia measurement times in terms of clotting time, PT, TT and aPTT. However, in this group BMBT was found to be shorter at T_1 measurement time compared to the D/P group. It has been thought that remifentanil causing a decrease in heart rate and cardiac output as well as its strong hypotensive effects (Beier et al., 2015; Gimenes et al., 2011; Murrell et al., 2005; Pei et al., 2014) may have played a role in this difference emerging. The vasodilatation occurring in the blood vessels is also effective in shortening bleeding time (Binici et al., 2015) by affecting blood viscosity.

A prolonged aPTT in spite of normal prothrombin time indicates the deficiency of factors VIII (Haemophilia A and von Willebrand Disease), IX and XI. Prolongation of both PT and aPTT suggests deficiency of common path coagulation factors (factor X, V and II) or qualitative or quantitative fibrinogen disorder or inhibition (Giurgiu et al., 2009). Lengthening of the PT value alone may be observed in extensive intravascular coagulation, hepatic diseases or patients with Vit K deficiency (Ogurtan et al., 2002). In this study, a statistically significant lengthening was determined in the PT value at measurement time T_1 in the D/R group compared to the D/P group. However, no difference was observed in the aPTT levels in either group. Pre-anaesthesia biochemical analysis was performed in all cases and liver function tests indicated AST and ALT values to be within the normal range. In the authors' opinion, while the PT prolongation emerging only after anaesthesia in the DR group did not develop as a result of liver function disorder, the reason for this lengthening could not be explained, in view of the fact that when evaluated within the group, no statistically significant difference was found between either T_0 or T_1 in terms of PT values.

In a study (Ogurtan et al., 2002) investigating Diazepam/Ketamine combination, it was reported that this combination had

no significant effect on aPTT or BMBT, whereas it caused a significant lengthening in the PT value. In the same study, it was stated that Xylazine/Ketamine combination caused prolongation in aPTT and PT (Ogurtan et al., 2002). In the present study, within-group measurement times in the D/P and D/R groups showed no changes in terms of these parameters. However, when the groups were compared, it was found that only the PT value was longer in the D/R group, compared to the other group. At the same time, in the propofol group, different to the anaesthesia protocols mentioned above, it was evaluated that the reason for PT not lengthening was due to either the antioxidant properties of propofol (Lee, 2012) or the fact that propofol had no adverse effect on thrombocyte function or the coagulation process (Kamal and Kamal, 2008). As a result of this data, while concluding that general anaesthesia is effective on PT, it must be stated that more advanced analysis is required to fully explain the mechanism.

In the D/P group, it was determined that anaesthetic drug administration and the endotracheal intubation procedure did not have a sufficiently significant effect on blood pressure and therefore blood flow rate, to cause coagulation factors to be affected. This finding was evaluated as occurring in relation to the antioxidant properties of propofol (Lee, 2012) or the fact that it has no adverse effect on thrombocyte function or the coagulation process (Kamal and Kamal, 2008).

In dogs, prolonged bleeding time occurs in relation to thrombocytopenia, von Willebrand disease, uremia, aspirin or dextran use and long-term carbenicillin treatment (Forsythe and Willis, 1989; Smith et al., 2005). In this study, no difference was observed either within groups or between groups in terms of bleeding time in either the D/P or D/R group. This data was associated both with the fact that thrombocyte counts were within physiological limits as well as the lack of long-term drug administration in the dogs assessed.

While it is stated that neuroleptanalgesia produces reliable anaesthesia induction in unwell patients, based on the data obtained at the end of the study, it was determined that D/P combination is more reliable in the anaesthesia of patients requiring surgical intervention.

Ethics Committee Approval: The study was conducted in accordance with the ethical principles approved by İstanbul University Animal Experiments Local Ethics Committee (26.04.2018/2018/38).

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