Effect of xylazine-ketamine and diazepam-ketamine anesthesia on activated partial thromboplastin time, prothrombin time and bleeding time in dogs

Z. OGURTAN, C. CEYLAN, H. IPEK and C. IZCI

Summary

The effects of xylazine-ketamine and diazepam-ketamine on activated partial thromboplastin time (APTT), prothrombin time (PT) and buccal mucosa bleeding time (BMBT) were evaluated in dogs. Altered APTT, PT and BMBT values were found in xylazine-ketamine and diazepam-ketamine anesthesia. Comparison of xylazine-ketamine to diazepam-ketamine revealed a significant increase for APTT, PT at 30, 60 and 90 minutes and for BMBT at 30 and 60 minutes.

Key-words: dog - APTT - PT - xylazine-ketamine - diazepam - ketamine.

Introduction

Activated partial thromboplastin time (APTT), evaluating intrinsic and prothrombin time (PT), evaluating extrinsic pathway of coagulation cascade, are generally used to monitor coagulation disorders and administration of coagulation therapy [32, 36]. Causes of prolonged APTT include factor deficiencies (von Willebrand’s disease, haemophilia A (Factor VIII deficiency), and haemophilia B (Factor IX deficiency) and the presence of circulating anticoagulants [4, 11, 29, 36]. The APTT test is the most commonly used coagulation assay in monitoring heparin effects in persons [8] and has been also recommended in dogs [9]. Prolongation of PT as caused by deficiencies of factors (VII, V, X, II) and fibrinogen [22, 36] is the most common coagulation abnormalities seen in cats [21]. The PT may be prolonged in patients with disseminated intravascular coagulation (DIC), liver diseases, or vitamin K deficiency [4, 11, 29, 36].

Prolongation of APTT and PT was found in dogs with hepatic degeneration, inflammation, cirrhosis and neoplasia [2]. Hepatic disease causes abnormalities of the coagulation system [2, 3]. Disseminated intravascular coagulation (DIC) which prolongs APTT and PT [15], is a well recognized complication of neoplasia in dogs [7, 12, 17, 30] and is the most common defect associated with bleeding in neoplastic formations [3, 7, 19, 30] and during surgery [14].

The effects of xylazine-ketamine and diazepam-ketamine induced anesthesia on the APTT, PT and buccal mucosa bleeding time (BMBT) are not known. The purpose of this study was to see if the injectable anesthetics could be used on patients with coagulopathies undergoing surgery and to search the most suitable anesthetic combination less affects the coagulation parameters and to see if these anesthetic protocols could be used on the determination of coagulation assays on those patients with coagulopathies or tendency for coagulopathies under surgical intervention.

Materials and methods

The protocol for this study was approved by the Selçuk University Committee on animal use and care. A total of 12 mature and either sex of dogs was used in this study and divided into two groups. The dogs in xylazine-ketamine group received 2 mg/kg of xylazine hydrochloride (Rompun, Bayer) and 5 minutes later, they had 20 mg/kg of ketamine hydrochloride (Ketalar, Parke-Davis). The dogs in diaze-
pam-ketamine group had 0.5 mg/kg of diazepam (Diazem, Deva) 5 minutes prior to injection of 20 mg/kg of ketamine hydrochloride. All the dogs received half the dose of ketamine hydrochloride at the 60th minute of anesthesia. All combinations were given intramuscularly.

Venous blood samples were taken from the jugular vein and mixed in the proportion of 1 part 3.8 % sodium citrate to 9 parts blood and centrifuged at 3000 rpm for 15 minutes. Blood samples were collected prior to anesthesia as a control and at 30, 60 and 90 minutes. APTT and PT were measured on freshly separated plasma with commercial reagents for human blood coagulation test by Behnk Elektronik (Organon Teknika, Thrombolyser Compact XR), within 30 minutes after the samples were collected. Using lancet, a penetration was made on the upper lip to measure the BMBT through a filter paper every 10 seconds 1 to 2 mm below the puncture to prevent the disturbance of the penetration and therefore bleeding time until no blood appeared on the filter paper, at the same time intervals. Student’s t test was used for statistical analysis and p ≤ 0.05 was considered to be significant.

Results

Xylazine-ketamine combination caused statistically significant (p ≤ 0.05) prolongation for the APTT at 30, 60 and 90 minutes compared to the control value. A statistically significant (p ≤ 0.05) decrease (still above the control value) was observed for the APTT at 60 and 90 minutes compared to that at 30 minutes in the xylazine-ketamine group. Diazepam-ketamine combination had no significant effect with slight increase for the APTT during the anesthesia compared to the control value and between time intervals. There was a significant increase (p ≤ 0.05) for the APTT at 30, 60 and 90 minutes in the xylazine-ketamine group compared to that in the diazepam-ketamine group (Table I).

Xylazine-ketamine prolonged the PT significantly (p ≤ 0.05) at 30, 60 and 90 minutes compared to the control value. The difference for the PT was also significant (p ≤ 0.05) at all time intervals except between 60 and 90 minutes. Xylazine-ketamine combination caused a significant (p ≤ 0.05) decrease (still above the control value) for the PT at 60 and 90 minutes compared to that at 30 minutes. Diazepam-ketamine combination had significantly (p ≤ 0.05) increased the PT at 30, 60 and 90 minutes compared to the control value. Diazepam-ketamine had decreased the PT insignificantly at 90 minutes (still above the control value) compared to that at 60 minutes and increased the PT insignificantly at 90 minutes (still above the control value) compared to that at 30 minutes. Comparison of xylazine-ketamine to diazepam-ketamine on the effect of PT had significant differences (p ≤ 0.05) at 30, 60 and 90 minutes (Table II).

Xylazine-ketamine anesthesia prolonged the BMBT with significant differences (p ≤ 0.05) occurring at 30 and 60 minutes compared to the control value, and decreased the BMBT significantly (p ≤ 0.05) at 90 minutes compared to 30 and 60 minutes. Although the BMBT shortened insignificantly at 90 minutes compared to the control value, it was still above the control value.

Diazepam-ketamine had slight prolongation for the BMBT during the anesthesia with a decrease (still above the control value) at 60 and 90 minutes compared to that at 30 minutes. Comparison of xylazine-ketamine to diazepam-ketamine on the effect of the BMBT had significant differences (p ≤ 0.05) at 30 and 60 minutes. That difference was not significant at 90 minutes (Table III).

Discussion

Although xylazine-ketamine combination caused a significant prolongation of the APTT and PT at all time intervals compared to the control value, there was a decrease (still above the control values) for the APTT and PT at 60 and 90 minutes compared to those at 30 minutes. On the other hand, diazepam-ketamine combination had an insignificant

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control*</th>
<th>TIME (sec) (during anesthesia)</th>
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<tbody>
<tr>
<td></td>
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<td></td>
<td></td>
<td>90</td>
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<tr>
<td>Xylazine-ketamine</td>
<td>16.67 ± 1.03a</td>
<td>22.83 ± 2.14b, x</td>
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<td></td>
<td>20.83 ± 0.98c, x</td>
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<td>19.00 ± 1.27d, x</td>
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<td>Diazepam-ketamine</td>
<td>15.67 ± 1.03a</td>
<td>16.23 ± 0.98a, y</td>
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<td>16.35 ± 0.75a, y</td>
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<td>16.50 ± 1.05a, y</td>
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* : As base-line
Values are Mean ± SD. Different superscript letters denote significant (p ≤ 0.05) differences within the same column and between groups (x, y) on the same column, n = 6 in each group.

Table I. — Activated partial thromboplastin time (seconds) values in xylazine-ketamine and diazepam-ketamine anesthesia.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control*</th>
<th>TIME (sec) (during anesthesia)</th>
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<tr>
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<td>60</td>
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<td>90</td>
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<tr>
<td>Xylazine-ketamine</td>
<td>9.33 ± 0.82a</td>
<td>14.67 ± 0.82b, x</td>
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<td></td>
<td></td>
<td>13.83 ± 1.17c, x</td>
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<tr>
<td></td>
<td></td>
<td>12.83 ± 0.98c, x</td>
</tr>
<tr>
<td>Diazepam-ketamine</td>
<td>8.83 ± 1.17a</td>
<td>10.67 ± 1.75b, y</td>
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<td></td>
<td></td>
<td>11.17 ± 0.75b, y</td>
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<tr>
<td></td>
<td></td>
<td>11.00 ± 0.89b, y</td>
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</tbody>
</table>

* : As base-line
Values are Mean ± SD. Different superscript letters denote significant (p ≤ 0.05) differences within the same column and between groups (x, y) on the same column, n = 6 in each group.

Table II. — Prothrombine time (seconds) values in xylazine-ketamine and diazepam-ketamine anesthesia.
prolongation of the APTT at all time intervals and there was a significant prolongation of the PT during the anesthesia compared to the control value with a slight decrease observed at 90 minutes. Comparison of the xylazine-ketamine to diazepam-ketamine revealed significant increase both for the APTT and PT at all time intervals. It was reported that APTT and PT tests are sufficient enough to make a decision. If both are negative further investigation of the coagulation system is ignored [32]. APTT and PT are considered to be prolonged if their time is more than 4 seconds [24]. Based on this, the prolongation of the APTT and PT which is (> 4 seconds) at 30 and 60 minutes compared to the controls in the xylazine-ketamine group, could be considered as notably to change the coagulation parameters in our study. Although the prolongations (< 4 seconds) were statistically significant for the rest of the intervals, these parameters may increase and/or alleviate the prolongation on those patients with coagulopathies under surgical interventions.

The reason for the prolongation of the APTT and PT occurred in our study, is not known. Slight prolongation of APTT and PT was found in the xylazine-ketamine group in rats anesthetized with intraperitoneal administration of the drugs which were supplemented as necessary and the reason for the prolongation could not be explained [35]. The APTT screens the coagulation factors except factors VII and XIII [22]. The PT evaluates the extrinsic pathway of coagulation disorders (factors VII, X, V, II and fibrinogen) [22]. Fibrinogen degradation products change the APTT and PT levels [27]. The PT and APTT begin to prolong when individual factor levels fall below 25 %, and 25 to 40 %, respectively [5]. The differences on the prolongation of the APTT and PT occurred in our study, might be resulted from deficiency of one or more of the intrinsic pathway for the APTT and abnormalities of the extrinsic pathway as factors VII, X and X, prothrombin and fibrinogen for the PT.

Surgical patients with hepatic disease, including degeneration, inflammation, cirrhosis and neoplasia generally bleed extensively with alterations on APTT, PT and factors IX, XI, VIII [2]. The most common cause of DIC is mammary carcinoma [23, 26], intestinal lymphosarcoma [17], hemangiomas [14], hemangiosarcomas [13, 14] ovarian, testicular, pulmonary, pancreatic, gastric, gall-bladder, colonic and pancreatic carcinomas [6], pancreatitis [7] cirrhosis, cesarean section [6] and gastric-dilation-volvulus in dogs [22, 25]. Neoplasms of skin, bone, thyroid gland, oropharynx and nasal cavity have also an effect on alterations on APTT and PT resulting from DIC [23]. Mammary carcinomas have been associated with haemostatic abnormalities of mainly APTT, PT [26], platelet count and factors (V, VIII and X) [34]. Surgical correction is indicated in liver cirrhosis in man [10, 16], in dogs [6] and in a variety of conditions in animals. Patients with hepatic disease requiring surgical interventions are at increased preoperative risk [10]. Therefore, the effects of anesthetics on coagulation parameters have to be taken into consideration on patients undergoing surgery. These cases must be approached with extreme caution to alleviate the already altered coagulation parameters.

An increase observed for the BMBT, was insignificant in the diazepam-ketamine group at all time intervals in our study. The increase for the BMBT was significant at 30 and 60 minutes compared to the control and there was a significant decrease for the BMBT at 90 minutes compared to 60 minutes in the xylazine-ketamine combination. Comparison of the xylazine-ketamine to diazepam-ketamine with regard to the BMBT had significant increases at 30 and 60 minutes. Although it was reported that determining the APTT alone for the predictor of hemorrhage preoperatively was found to be important [33], prolonged APTT alone is not always related to a bleeding risk [1]. This is in accord with our study that insignificant prolongation of the APTT itself, had no significant effect on the BMBT in the diazepam-ketamine group. On the other hand significant prolongation of both the APTT and PT at all time intervals, (especially at 30 and 60 minutes at which, prolongation is > 4 sec) compared to the controls resulted in a significant increase for the BMBT in the xylazine-ketamine group. Supplementation of the anesthesia with ketamine at 60 minutes had no significant effect on the BMBT in the diazepam-ketamine group. On the other hand significant prolongation of both the APTT and PT at all time intervals, (especially at 30 and 60 minutes at which, prolongation is > 4 sec) compared to the controls resulted in a significant increase for the BMBT in the xylazine-ketamine group. Supplementation of the anesthesia with ketamine at 60 minutes had no significant effect on the BMBT in the diazepam-ketamine group.

**Table III. — Bleeding time (minutes) in xylazine-ketamine and diazepam-ketamine anesthesia.**

<table>
<thead>
<tr>
<th>Groups</th>
<th>Control*</th>
<th>30</th>
<th>60</th>
<th>90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xylazine-ketamine</td>
<td>2.25 ± 0.27a</td>
<td>2.90 ± 0.49b, x</td>
<td>3.2 ± 0.41b, x</td>
<td>2.33 ± 0.26a, x</td>
</tr>
<tr>
<td>Diazepam-ketamine</td>
<td>1.92 ± 0.38a</td>
<td>2.20 ± 0.52a, y</td>
<td>2.17 ± 0.42a, y</td>
<td>2.00 ± 0.32a, x</td>
</tr>
</tbody>
</table>

* : As base-line
Values are Mean ± SD. Different superscript letters denote significant (p ≤ 0.05) differences with time (a, b, c, d) on the same line and between groups (x, y) on the same column, n = 6 in each group.
xylose and diazepam, but no changes were observed for BMBT in dogs tranquilized with xylazine [18, 28]. The bleeding is the screening test for platelet function. Reduced number of platelets was observed in xylazine alone given to sheep [31]. In vitro antiplatelet effects of halothane, and nitrous oxide were also reported [37]. Altered platelet counts might be seen for patients with or without coagulopathies undergoing surgical interventions [20] which is in agreement with our findings that changes observed would aliterate the already altered parameters under anesthesia.

It would be wise to use antiplatelet agents with the known effects on APTT and PT in patients with coagulopathies or at risk for bleeding disorders. This study also highlights the importance of the effects of injectable anesthetics to be taken into consideration on patients with or without coagulopathies under surgical operations. It would also be interesting to see the effects of intubation anesthetics on APTT and PT and other coagulation assays in future since these antiplatelet agents provide longer duration of anesthesia.

References