AN EXPERIMENTAL STUDY ON THE EFFECTS OF KETAMINE AND PROPOFOL ANESTHESIA ON CERTAIN HEMOSTATIC INDICES IN DOGS

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SUMMARY

The effects of ketamine and propofol anesthesia on certain hemostatic parameters was investigated in dogs premedicated with atropine sulphate, diazepam and xylocaine Hcl. Obtained results revealed that, after induction of anesthesia with ketamine, a significant decrease in Prothrombin Time (PT) and platelets count were observed. A significant increase in Activated Partial Thromboplastin Time (APTT) was also recorded. However, no significant alteration in fibrinogen concentration was detected. Concerning propofol anesthesia, a significant decrease in PT was recorded. No obvious alterations in APTT, fibrinogen concentration, and platelet count were detected.

Conclusively, Propofol as an anesthetic agent can be administered safely in disturbed hemostatic conditions.

INTRODUCTION

Hemostasis, the process by which bleeding is arrested, involves a complex series of physiological and biochemical interaction between the blood vessels wall, platelets, blood coagulation elements and fibrinolysis. The success of any surgical procedures is mainly dependent upon adequate hemostasis (Troy, 1988).

Blood coagulation is a part of an important host defense mechanism. Upon vessel injury, platelet adheres to macromolecules in subendothelial tissue at the site of injury and then aggregate to form the primary hemostatic plug. Normal hemostasis occurs as the result of regulated processes to accomplish two function, first, it maintains blood in a fluid and clot free state, second, it induces a rapid and localized hemostatic plug at the site of vascular injury (Kumar et al, 2005). The hemostatic process includes three phases which are:
-Primary hemostasis (vasoconstriction and platelet clot formation)
-Coagulation and
-Fibrinolysis.
In this study, the minimum coagulation profile for assessment of hemostatic mechanisms consisting of Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), fibrinogen and Platelet count was sufficient enough to detect the patients at risk of bleeding.

Ketamine was synthesized in 1962 by Stevens and was first used in human by Corssen and Domino 1966. It was proved to be the most promising in laboratory animal testing (Gerald et al., 2006). Ketamine is metabolized by hepatic microsomal enzyme to form norketamine which is then hydroxylated to hydroxy norketamine. These products are conjugated to water-soluble glucuronide derivatives and are excreted in urine. Ketamine in combination with xylocaine Hcl has been used as dissociative anesthesia in dogs.

Ketamine Hcl caused moderate hypercoagulative changes in the hemostatic system and a drastic increase in fibrinolysis (Laux and Seiffge, 1993).

Propofol (2,6-disopropylphenol) is one of the alkyl phenols derivatives. Propofol is rapidly metabolized in the liver by conjugation to glucuronide and sulfate to produce water soluble compound. Propofol induce induction and maintenance of anesthesia by continous IV infusion or intermittent bolus. Rapid metabolism, lack of any cumulative effect and smooth rapid recovery made propofol the drug of choice for total intravenous anesthesia (TIVA) (Zoran et al., 1993 and Branson and Gross, 2002).

The clearance of propofol from blood is controlled mainly by intra hepatic, in addition to, extra hepatic metabolic processes. The high clearance of propofol than the capacity of the liver in respect of its total blood supply, suggests that extra hepatic mechanisms are contributing to the clearance of propofol from blood (Simons et al.; 1985; Servin et al., 1990, and Kirrela et al., 2000).

The assessment of platelets and coagulation elements after anesthesia with propofol indicated no significant alternations either on platelets count or on coagulation pathways. In addition, no evidence that propofol adversely affects hepatic and renal functions (Niccoloil et al., 1992 and Haberer, 1994).

The present investigation was done to clarify whether ketamine Hcl and propofol cause in vivo alterations in blood coagulation.
MATERIAL AND METHODS

Experimental animals:

The study was carried out on 14 intact male mongrel dogs with an age ranged between 1.5-2.5 years and weighing 12-14kg. Animals were randomly allocated into 2 equal groups. Physical examination of dogs prior to the study was found to be normal.

Experimental design:

Food withdrawal was done 12hrs before the experiment. Water was removed one hour before induction of anesthesia. A cephalic and Jugular veins were percutaneously catheterized, the former one for IV injection of ketamine Hcl and propofol, and the other one for collection of blood samples. All dogs were per medicated by atropine sulphate (0.1mg/kg BW) subcutaneously 15 minute before anesthesia, diazepam (0.5mg/kg BW) and xylocaine Hcl (1.5mg/kg BW) intravenously just before induction of anesthesia.

**Group I**: Ketamine 5% solution was injected in a dose of 5.5mg/kg BW I/V for induction of anesthesia and anesthesia was maintained by continuous infusion of ketamine in a dose of 1-3 mg/kg/hr.

**Group II**: Anesthesia was induced by propofol 1 % solution in a dose of 2.5mg/kg BW for induction and 0.3mg/kg/min. for maintenance.

Blood Samples collection:

For coagulation studies; 4.5ml blood collected into glass tubes containing 0.5ml sodium citrate 3.8%. The samplings began before drug administration (Time 0) and were continued at 15, 30, 45, 60, 90 and 120 minutes after injection. The catheter was flushed with 5ml saline solution after samples collections to replace lost fluid volume and maintained catheter patency. Citrated plasma was obtained and used for determination of prothrombin Time (PT), Activated partial thromboplastin time (APTT) and fibrinogen concentration according to the method of Dacie and Lewis, (1991) using commercial reagents obtained from DiaMed; Switzerland and the Bio-Meriewx Fibrometer. Platelet count was done by using EDTA blood samples (Dacie and Lewis, 1991).

Obtained data were statistically analyzed by using student "t" test according to Snedecar and Cochrane (1980).
RESULTS

Table (1) shows the results of coagulation parameters carried out in dogs receiving ketamine Hcl. A significant decrease of PT following anesthesia was recorded by 15, 30, 45, 60, 90 and 120 minutes (P≤0.5) in relation to preanesthetic values (Fig. 1). A significant increase in APTT following anesthesia by 15, 30 and 45 minutes (P≤0.01) in relation to the baseline values (Fig. 2). Also, in the same group, there was a significant decrease of platelets count following anesthesia by 15, 30, 45 minutes (P≤0.01) and 60 minutes (P≤0.05) in relation to the preanesthetic values (Fig. 3). However, no significant differences were recorded in fibrinogen concentrations all over the experimental time (Fig. 4).

Table (2) illustrates the obtained results concerning propofol anesthesia. A significant decrease in PT following anesthesia by 30, 45, 60, 90 and 120 minutes (P≤0.05) in relation to the baseline values were recorded. (Fig.1) Also, there were no statistically significant differences between any of the values of APTT (Fig. 2), fibrinogen concentration (Fig. 4), and platelets count in relation to the preanesthetic readings (Fig. 3).

Table (1): Some coagulation parameters in dogs following Ketamine Anesthesia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Time</th>
<th>PT / sec</th>
<th>APTT/sec</th>
<th>Fibrinogen conc. Mg/dl</th>
<th>Platelets count x 1000/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre anesthetic (0-time)</td>
<td>9.00±0.30</td>
<td>17.70±0.25</td>
<td>570 ±1035</td>
<td>375 ±9.00</td>
</tr>
<tr>
<td></td>
<td>15 minutes</td>
<td>7.50±0.35(*)</td>
<td>19.80±0.22(**)</td>
<td>650 ±15.50</td>
<td>310 ± 3.50(**)</td>
</tr>
<tr>
<td></td>
<td>30 minutes</td>
<td>7.25 ±0.30(*)</td>
<td>19.70±0.30(**)</td>
<td>570 ±9.80</td>
<td>280 ± 3.15(**)</td>
</tr>
<tr>
<td></td>
<td>45 minutes</td>
<td>7.50±0.12(**)</td>
<td>19.40±0.30(**)</td>
<td>575 ±6.70</td>
<td>295 ± 2.20(**)</td>
</tr>
<tr>
<td></td>
<td>60 minutes</td>
<td>7.30±0.10(**)</td>
<td>17.25±0.25</td>
<td>565 ±8.20</td>
<td>355 ± 300(**)</td>
</tr>
<tr>
<td></td>
<td>90 minutes</td>
<td>.40±0.10(*)</td>
<td>17.50±0.28</td>
<td>570 ±6.60</td>
<td>385 ± 6.00</td>
</tr>
<tr>
<td></td>
<td>120 minutes</td>
<td>.50±0.40(*)</td>
<td>17.40±0.35</td>
<td>575 ±1230</td>
<td>387 ± 3.10</td>
</tr>
</tbody>
</table>

Values are means ±SE.
(*) : significant at P ≤0.05.
(**) : significant at P ≤0.01.
(n): number of experimental Animals= 7.
**Fig.(1):** Prothrombin Time (PT) in dogs following Ketamine and Propofol Anesthesia Preoperatively (0-time), 15, 30, 45, 60, 90, and 120 min. respectively.

**Fig.(2):** Activated Partial Thromboplastin Time in dogs following Ketamine and Propofol Anesthesia, preoperatively (0-time) 15, 30, 45, 60, 90, and 120 min. respectively.
Table (2): Some coagulation parameters of dogs following propofol Anesthesia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PT / sec</th>
<th>APTT/sec</th>
<th>Fibrinogen conc. Mg/dl</th>
<th>Platelets count x 1000/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre anesthetic (0-time)</td>
<td>9.15±0.40</td>
<td>16.15±0.80</td>
<td>525±12.00</td>
<td>375±10.70</td>
</tr>
<tr>
<td>15 min</td>
<td>9.15±0.10(*)</td>
<td>17.45±0.40</td>
<td>530±7.00</td>
<td>385±10.04</td>
</tr>
<tr>
<td>30 min</td>
<td>7.30±0.20(*)</td>
<td>16.30±0.50</td>
<td>527±4.00</td>
<td>385±9.90</td>
</tr>
<tr>
<td>45 min</td>
<td>6.45±0.25(*)</td>
<td>14.30±0.40</td>
<td>520±10.00</td>
<td>360±10.12</td>
</tr>
<tr>
<td>60 min</td>
<td>7.45±0.40(*)</td>
<td>17.00±0.25</td>
<td>520±5.00</td>
<td>358±11.01</td>
</tr>
<tr>
<td>90 min</td>
<td>6.45±0.20(*)</td>
<td>17.30±0.70</td>
<td>510±5.20</td>
<td>352±14.60</td>
</tr>
<tr>
<td>120 min</td>
<td>6.45±0.30(*)</td>
<td>15.15±0.60</td>
<td>510±8.00</td>
<td>398±11.30</td>
</tr>
</tbody>
</table>

Values are means ±SE.

(*): significant at P ≤0.05.

(n): number of experimental Animals = 7.

Fig. (3): Platelet Count in dogs following Ketamine and Propofol Anesthesia, Preoperatively (0-time) 15, 30, 45, 60, 90, and 120 min. respectively.
Fig. (4) : Fibrinogen concentrations in dogs following Ketamine and Propofol anesthesia, preoperatively (0- time) 15, 30, 45, 60, 90,and 120 min. respectively.

DISCUSSION

Of all the problems, that confront surgeons, the most important is that of hemorrhage. It follows that the coagulation process has to be handled with great care. The another surgeon choose the four tests in the study as (Blue and short (1987) stated that a minimum coagulation profile consisting of PT, APTT, fibrinogen and Platelet count is sufficient to detect the patients at risk of bleeding.

Regarding the PT, it was statistically shortened from the preanesthetic values, following ketamine Hcl and propofol administration. The decrease in PT could be attributed to the local irritation of the vessels by anesthetic agents resulting in the release of tissue thromplastin activating the extrinsic clotting pathway (Badylack, 1988).

A significant increase in APTT was recorded after administration of ketamine Hcl, this increase lies in parallel with the decrease in platelet count. The increase in APTT may be related to the decrease in platelets. The platelets participate in the prothrombinase reaction which results in the enzymatic conversion of prothrombin to thrombin contributing in the activation of factor X and providing a surface for the contact phase of coagulation and generation of activated factor II (Rosing et al., 1985). The obtained decrease in APTT
contradicts the results of (Khrenov et al., 1991); and Laux a Seiffge (1993) who stated that ketamine Hcl caused hypercoagulative changes in the hemostatic system and drastic increase in fibrinolysis.

Ketamine Hcl is primarily extensively metabolized in the liver and this may be reflected on the production of coagulation factors, therefore, ketamine Hcl should probably not be used in individual's bordering on hepatic failure (Booth, 1999; Blue and Short, 1987).

In the ketamine group, the decrease in mean platelet count was previously noticed by (Maclntyre et al. 1985) and (Handagama and Feldman, 1988) who mentioned that thrombocytopenia develops within a few minutes after intravenous administration of drug. This decrease in the platelets is transient. The platelets normalize within 1 hour. This transient form is due to temporary sequestration of platelets in the liver. Also, platelets sequestration follows the increase in secretion of endogenous catecholamine’s after ketamine Hcl anesthesia.

According to the obtained results, it was observed that propofol did not alter blood coagulation parameters. This result coincides with that obtained by (Mayne et al. 1988); (Haberer, 1994) and (Mustola et al. 2000) who mentioned that propofol had no effect on blood coagulation; this may be attributed to the decreased adrenaline concentration following induction with propofol, in addition to extrahepatic component to the metabolism of the drug.

In conclusion, an obtained result does not support the use of ketamine Hcl for anesthesia in individuals suffering from coagulation disorders. However, propofol has no adverse effect on the process of blood coagulation and can be used safely in such conditions.

REFERENCES

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الملخص العربي

دراسة تجريبيّة على تأثيرات التخدير بعقار الكيتامين والبروبوفول على بعض مؤشرات وقف النزيف في الكلاب.

إجراء هذه الدراسة بالمشاركة مع قسم الفسيولوجي - كلية الطب البيطري - جامعة القاهرة.

استمرت هذه الدراسة على أربعة عشر كيلاً تتراوح أعمارهم ما بين العام والنصف إلى العامين والنصف وتتراوح أوزانهم من أثنا عشر إلى أربعة عشر كيلوجرام حيث تم تقسيمهم إلى مجموعتين وتشمل كل مجموعة على سبعة كلاب.

بعد التأكد من سلامتهم الطبية فيما قبل إجراء التخدير، تم منع الطعام عنهم أثنا عشرة ساعة قبل التخدير وتم منع الماء لمدة ساعة واحدة قبل التخدير.

الدراسة أجريت مع دواجن الكيتامين.

المجموعة الأولى: تم إجراء التخدير باستخدام عقار الكيتامين.

المجموعة الثانية: تم إجراء التخدير باستخدام عقار البروبوفول.

وتم قياس معاملات وقف النزيف كالاتي: - قبل إجراء التخدير، 15، 30، 45، 60، 90، 120 دقيقة بعد بدء التخدير.

وتم قياس الآتى:
- زمن البروثرومبين
- زمن الثرموبلاستين الجزئي النشيط
- الصفائح الدموية
- تركيز الفيبرينوجين.

وأثبتت هذه الدراسة عدم فاعليّة استخدام عقار الكيتامين مع وجود اضطرابات في معاملات وقف النزيف بينما أكدت الدراسة أنه يمكن استخدام عقار البروبوفول بامان في وجود اضطرابات في معاملات وقف النزيف.
The effects of ketamine and propofol anesthesia on certain hemostatic parameters was investigated in dogs premedicated with atropine sulphate, diazepam and xylocaine Hcl. Obtained results revealed that, after induction of anesthesia with ketamine, a significant decrease in Prothrombin Time (PT) and platelets count were observed. A significant increase in Activated Partial Thromboplastin Time (APTT) was also recorded. However, no significant alteration in fibrinogen concentration was detected. Concerning propofol anesthesia, a significant decrease in PT was recorded. Conclusively, Propofol as an anesthetic agent can be administered safely in disturbed hemostatic conditions. commonly used in general anesthesia. The relation between propofol and its effect on physiological variables is traditionally described by compartmental pharmacokinetics1 and pharmacodynamics2 (PKPD) models [21]. The PK model. GP K (s) relates the propofol infusion rate u(t) to the plasma concentration Cp(t). Studies quantifying the effect of propofol on blood pressure (BP) are limited [25], [26]. Extrapolation based on the ident. We identified a set of patient models describing the effect of propofol on BP [19] for a subset of the population requiring continuous BP monitoring using an arterial line. Continuous data during induction of anesthesia were available for model identification, providing adequate excitation for model identification. Our previous study suggested that propofol and alfentanil exhibit synergetic effects. The reported dose of propofol required to induce general anesthesia in dogs is approximately 4 mg/kg (Auckburally et al. 2008). In comparison, the mean dose of propofol in Group 1 was 4.1 mg/kg. (2001) studied the effects of fentanyl, alfentanil, remifentanil and sufentanil on the bispectral index during anesthesia with propofol in humans; no significant differences were observed between the fentanyl group and the placebo group. Hatzschbach et al. (2008) found that the addition of remifentanil did not change the bispectral index in dogs undergoing propofol-mediated anesthesia. Studies have shown that ketamine causes an increase in intraocular pressure [7], whereas propofol results in decreased intraocular pressure [4]. The purpose of this study was to compare the effects of propofol, ketamine and ketofol on intraocular pressure in New Zealand white rabbits. Materials and methods. ANIMALS Atatürk University Local Board of Ethics Committee for Animal Experiments has approved the study protocol of this research (HADYEK decision no: 2013/139). Eight, adult male, New Zealand white rabbits weighing 2.5-3.3 kg were used in this study. They were housed in individual cages