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# Effect of Thiopentone and Thiopentone-Vecuronium Total Intravenous Anaesthesia on Haematological, Biochemical and Electrocardiographic Parameters in Dogs

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## Abstract

The present study was conducted to evaluate the effect of thiopentone and thiopentone-vecuronium on various biochemical, haematological and electrocardiographic parameters. It was also aimed to evaluate the suitability of this combination for total intravenous anaesthesia. Animals were divided into two groups and both the groups were given atropine followed by diazepam and pentazocine. Induction and maintenance were carried with thiopentone in both the groups but additionally the second group received vecuronium once the surgical plane of anaesthesia was attained. Blood samples were collected at different time points for estimation of haemoglobin, hematocrit and leukocyte counts. Plasma was used for glucose, plasma urea nitrogen, insulin and cortisol estimation. P,QRS and T-wave amplitude; QRS, PR andQT-intervals and P-wave duration were also measured. There was a significant ($p$<0.05) decrease in haemoglobin, hematocrit and leukocyte count within group-A. However, the differences between the groups were insignificant. Plasma urea nitrogen and creatinine increased significantly ($p$<0.05) in group-A at 90-minute interval. Plasma glucose did not vary significantly from base value within groups. However, at 0 and 90 minutes group-B had higher glucose levels than group-A. Group-A showed significantly ($p$<0.05) higher value of cortisol at 90-minute interval. Insulin levels stayed higher than the base value in both groups. Significantly ($p$<0.05) higher P-wave amplitude at 10, 45, 60 minutes was measured in group-A. No significant change in P-wave duration was observed. PR interval, QRS amplitude and QRS duration, QT interval and T-wave amplitude did not show any major differences. The study suggests that the alteration in various biochemical parameters were the outcome of general stress and those in haematology were due to pooling of blood. Thus, the combination provides haematological, biochemical and electrocardiographic stability and thus may be considered safe for dogs.

**Keywords:** Anaesthesia, Vecuronium, Thiopentone, Dogs.

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## Introduction

Anaesthesia is an indispensable pre-requisite to most of the surgical interventions, both in humans and animals, so that the surgeon can perform a surgical intervention with maximum precision. Total intravenous anaesthesia (TIVA) may be an appealing alternative to the standard inhalational agents, more commonly used for several reasons.[1] In any surgical intervention, unconsciousness, insensitivity to pain, good muscle relaxation, freedom from reflex responses and loss of motor ability are mandatory.[2]Thiopentone is an ultra-short-acting barbiturate anaesthetic which depresses the central nervous system to produce hypnosis and anaesthesia without analgesia. Its ultrashort action is because of rapid

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distribution into muscle tissues and its localization in body fat.[3] Skeletal neuromuscular blocking agents (NMBA) can be very useful anaesthetic adjuncts in patients undergoing orthopaedic surgery. By the time patients are taken to surgery, better muscle relaxation is usually required to reduce various fractures. Vecuronium is currently the most specific neuromuscular blocking drug in clinical use and is more potent and shorter acting than pancuronium**.** It shows a low propensity to liberate histamine and possesses a negligible ganglionic blocking action, hence cardiovascular side effects are unlikely to be seen during its clinical use.[4] The present study was conducted to determine haematological, biochemical and electrographic stability in thiopentone and thiopentone-vecuronium TIVA anaesthesia in canine orthopaedic surgeries.

## *Materials and Methods*

### Chemicals

Atropine (Tropin) as atropine sulphate, thiopentone (Thiosol) as thiopentone sodium and vecuronium (Neovac) as vecuronium bromide were purchased from Neon Laboratories Ltd., Mumbai, India. Diazepam(Calmpose) and pentazocine (Fortwin) were purchased from Ranbaxy Laboratories Ltd., Ahmadabad, India.

### *Animals and experimental design*

A prospective randomized blinded study was conducted on 12 client-owned dogs of either sex (8 males and 4 females) weighing 19.25 ± 3.24 kg presented for orthopaedic surgeries (intra-medullary pinning and cross pinning). The dogs were divided randomly into two equal groups, designated as group A and B. Animals were restrained properly and pre-anaesthetic drugs were injected. Atropine was injected at 0.04 mg/kg body weight (s/c). After 10 minutes of administering atropine, diazepam was injected at the rate of 0.5 mg/kg body weight (i/v) in both groups. After 5 minutes of diazepam administration, pentazocine @ 1.5 mg/kg body weight (i/v) was administered in both groups. Induction was done with 5 % thiopentone @ 10 mg/kg (i/v) till effect and maintenance were done with 5 % thiopentone (i/v) as an intermittent bolus in both the groups. All animals were intubated after thiopentone induction. Additionally, group B was given vecuronium @ 0.04 mg/kg (i/v) after attaining surgical plane of anaesthesia. Blood samples were collected from the cephalic vein at 0 (baseline), 30, 60 and 90 minutes after the administration of the drugs for estimation of various haematological parameters. The blood samples were centrifuged at 3000 rpm for 5 min and plasma separated and stored at -20 °C until assayed for the biochemical parameters.

### *Techniques*

Haemoglobin was estimated using 0.1N HCl with the help of Sahli's haemoglobinometer. Haematocrit was estimated by the microhematocrit method and using haematocrit tube reader. Total leukocyte count was estimated by standard technique using Neubar's cell counting chamber. For differential leukocyte count, blood smears were prepared. The plasma urea nitrogen was estimated as per diacetyl monoxide (DAM) method, plasma glucose was estimated by glucose oxidase-peroxidase method and plasma creatinine concentration was estimated by alkaline picrate method using commercial kits supplied by Span Diagnostics Ltd., India. Cortisol and insulin were estimated by radioimmunoassay (RIA) procedure using commercially available RIA kits (Immunotech, Beckman-Coulter Company, Czech Republic). Electrocardiographic recordings at 1 mV and 50 mm/sec paper speed were made using ECG Machine (Cardioart 6108T, BPL Ltd., India) on a lead II system to assess the cardiac function by using 3 lead system.

### *Statistical analysis*

The data were analysed for statistical significance using SPSS software version 16.0 (SPSS, Inc., Chicago, IL). One way analysis of variance and Duncan's Multiple Range Test (DMRT) was used to compare the means at different time intervals among different groups. Paired "*t*" test was used to compare the mean values at different intervals with their base values in each group. In each analysis, the differences were considered significant at a value of $p<0.05$.

## Results

### Haematological observations

### Haemoglobin (Hb)

In group A, Haemoglobin (Hb) decreased significantly ($p<0.05$) at 30 min interval from its baseline value with a further decrease at 60 min and 90 min interval. In group

**Table 1** Mean±SE values of various haematological parameters in groups A and B at different intervals

| Parameter | Group | Interval (minutes) | | | |
|---|---|---|---|---|---|
| | | 0 | 30 | 60 | 90 |
| **Haemoglobin (g/l)** | A | 111.67$^{ab}$±4.59 | 103.33*$^{ab}$±5.11 | 101.17$^{ab}$±7.40 | 98.33*$^{ab}$±6.01 |
| | B | 118.33$^{b}$±3.07 | 108.50$^{b}$±4.82 | 105.00$^{b}$±5.16 | 105.00 $^{b}$±5.00 |
| **Packed cell volume (l/l)** | A | 0.40±0.03 | 0.39±0.04 | 0.36*±0.04 | 0.35*±0.04 |
| | B | 0.38±0.02 | 0.36±0.01 | 0.36±0.01 | 0.35*±0.02 |
| **Total leucocyte count (x10$^9$/l)** | A | 11.54±1.00 | 9.76*±0.90 | 8.78±1.13 | 7.98*±0.95 |
| | B | 9.33±0.56 | 9.85±0.37 | 9.88±0.75 | 9.12±0.60 |
| **Lymphocyte count (%)** | A | 35.33 $^{ab}$±2.22 | 31.83** $^{ab}$±1.99 | 30.83*$^{bc}$±0.98 | 31.33±1.09 |
| | B | 37.83$^{b}$±0.95 | 34.00*$^{b}$±0.86 | 32.50**$^{c}$±0.62 | 33.00**±0.89 |
| **Neutrophill count (%)** | A | 64.67$^{ab}$±2.22 | 68.17**$^{ab}$±1.99 | 69.17*$^{ab}$±0.98 | 68.67±1.09 |
| | B | 62.17$^{a}$±0.95 | 66.00*$^{a}$±0.86 | 67.50**$^{a}$±0.62 | 67.00**±0.89 |

*Significantly different from base value (P<0.05); **significantly different from base value (P<0.01); Values with different alphabets differ significantly at respective intervals (P<0.05)

B, a non-significant ($p$>0.05) decrease was recorded at all time intervals. No significant ($p$>0.05) difference was seen between the groups at different time intervals. The data are given in table 1.

## *Packed cell volume (PCV)*

In group A, a non-significant ($p$>0.05) decrease was recorded at 30 min interval after the drug administration, thereafter, it decreased significantly ($p$<0.05) at 60 and 90 min intervals from the baseline value. In group B, a non-significant ($p$>0.05) decrease was seen at 30 and 60 min interval after the drug administration. Thereafter, it decreased significantly ($p$<0.05) at 90 min interval.

## *Total Leukocyte count (TLC)*

In group A, a significant (p<0.05) decrease was recorded at 30 min interval after the drug administration. It decreased further non-significantly ($p$>0.05) at 60 min interval and thereafter, decreased significantly ($p$<0.05) at 90 min interval. In group B, TLC values remained near the baseline and no significant difference($p$>0.05) was recorded at any interval of time.

## *Neutrophils*

In group A, a significant ($p$<0.01) increase was recorded at 30 min interval after the drug administration, which increased further significantly ($p$<0.05) at 60 min interval and thereafter, decreased non-significantly ($p$<0.05) at 90 min interval but remained higher than the baseline value. In group B, a significant ($p$<0.05) increase was recorded at 30 min interval after the drug administration. Thereafter, a highly significant ($p$<0.01) increase at 60 min and 90 min interval was recorded.

## *Lymphocytes*

In group A, a significant ($p$<0.01) decrease was recorded at 30 min interval after the drug administration, which decreased further significantly ($p$<0.05) at 60 min interval and thereafter, increased non-significantly ($p$> 0.05) at 90 min interval, but remained lower than the baseline value. In group B, a significant decrease ($p$<0.05) was recorded at 30 min interval after the drug administration which decreased further significantly ($p$<0.01) from 60 min to 90 min interval.

**Table 2** Mean±SE values of various biochemical parameters in groups A and B at different intervals

| Parameter | Group | Interval (minutes) | | | |
|---|---|---|---|---|---|
| | | 0 | 30 | 60 | 90 |
| Plasma urea nitrogen (mmol/l) | A | 6.52±1.22 | 6.13±0.41 | 8.27±1.33 | 9.11*±1.38 |
| | B | 5.52±0.84 | 5.65±0.75 | 7.43±0.98 | 9.51±1.49 |
| Creatinine (µmol/l) | A | 76.54±14.62 | 89.40*±14.05 | 117.57[a]±26.55 | 105.34*[ab]±20.64 |
| | B | 70.91±12.01 | 93.30±21.58 | 99.52*[a]±19.18 | 90.17*[ab]±12.38 |
| Cortisol (nmol/l) | A | 129.49±23.99 | 181.59±45.10 | 193.85±35.82 | 223.04*±37.92 |
| | B | 158.47±7.82 | 160.29±19.82 | 148.98±19.07 | 149.92±14.77 |
| Glucose (mmol/l) | A | 5.78[a]±0.24 | 5.99±0.25 | 5.94±0.27 | 6.08[a]±0.20 |
| | B | 8.71[b]±0.94 | 7.30±1.40 | 8.88±0.75 | 8.39[b]±0.51 |

*Significantly different from base value (P<0.05); Values with different alphabets differ significantly at respective intervals (P<0.05)

## Biochemical observation

### Plasma urea nitrogen (PUN)

In group A, non-significant ($p$>0.05) decrease of PUN was recorded at 30 min interval after the drug administration. The value increased non-significantly ($p$>0.05) at 60 min interval, thereafter, it increased significantly ($p$<0.05) at 90 min interval. In group B, PUN values increased non-significantly ($p$>0.05) at all intervals from its base value. The biochemical data are given in table 2.

#### *Plasma creatinine*

In group A, a significant ($p$<0.05) increase in plasma creatinine was recorded at the 30 min interval after the drug administration. Further, the value increased non-significantly ($p$>0.05) at 60 min interval, thereafter, it increased significantly ($p$<0.05) at 90 min interval. In group B, creatinine value increased non-significantly ($p$>0.05) at 30 min interval after the drug administration. Thereafter, creatinine increased significantly ($p$<0.05) up to 90 min interval and remained higher than the baseline values. Comparison between the groups revealed a non-significant ($p$>0.05) difference in creatinine concentrations at all intervals.

#### *Plasma glucose*

In group A and B, plasma glucose value did not vary significantly ($p$>0.05) from the baseline value up to the 90 min interval. Comparison between groups revealed a significantly ($p$<0.05) lower value of plasma glucose at 0 and 90 min intervals in group A than group B.

#### *Plasma cortisol*

In group A, plasma cortisol values increased non-significantly ($p$>0.05) up to 60 min interval in comparison to base value, thereafter, increased significantly ($p$<0.05) at 90 min. In group B, a non-significant ($p$>0.05) change in plasma cortisol was recorded at all intervals from the baseline value.

#### *Plasma insulin*

In group A, plasma insulin value increased significantly ($p$<0.05) up to 30 min interval in comparison to base value, however, at 60 min ($p$<0.05) and 90 min ($p$<0.01) it decreased significantly, but values remained higher than the baseline values. In group B, a non-significant ($p$>0.05) change in plasma insulin was recorded at all intervals from the baseline value, however, values remained higher than the baseline values

## Electrocardiography

### P-wave amplitude and P-wave duration

In all the animals, P-wave was positive at all intervals. In

group A, P wave amplitude increased non-significantly ($p$>0.05) at 10 min interval in comparison to base value, however, it returned to base value at 20 min, thereafter, it increased significantly ($p$<0.05) at 30 min as compared to its baseline value. Non-significant ($p$>0.05) increase in P-wave amplitude was recorded at 45 min. Increase in P-wave amplitude became significant ($p$<0.05) at 60 min interval. In group B, non-significant ($p$>0.05) decrease of P-wave amplitude was recorded at10 min interval followed by a significant ($p$<0.05) increase at 20 min interval from the baseline value. Thereafter P-wave amplitude increased non-significantly ($p$>0.05) at 30 min from its baseline value. P-wave amplitude value returned towards baseline value at 45 and 60 min intervals. Comparison between groups revealed a significantly ($p$<0.05) higher P-wave amplitude values at 10, 45 and 60 min interval in group A than group B. There were non-significant changes in P-wave duration in both the groups at all time intervals after drug administration from their respective base values. Various ECG indices are shown in table 3.

### *P-R interval*

There were non-significant ($p$>0.05) changes in the P-R interval in group A and B at all time intervals after drug administration from their respective base values. Comparison among groups revealed non-significant ($p$> 0.05) differences in P-R interval values in group A and B at all time intervals.

### *QRS complex amplitude and QRS complex duration*

In animals of group A, QRS complex amplitude increased non-significantly ($p$>0.05) from 10 min interval in comparison to base value, till the end of observation period. In group B, QRS complex amplitude increased non-significantly ($p$>0.05) at 10 min interval in comparison to base value. Thereafter, it decreased non-significantly ($p$>0.05) at 20 and 30 min interval from the baseline value. It showed a non-significant ($p$>0.05) increase at 45 min interval followed by a non-significant ($p$>0.05) decrease at 60 min interval from its baseline value. There were non-significant ($p$> 0.05) changes in QRS complex duration in all groups at all time intervals after drug administration from their respective base values.

### *QT interval*

In groups A, QT interval showed non-significant ($p$> 0.05) changes at all intervals except at 20 min where significant ($p$<0.05) decrease was recorded after drug administration from the base values. In groups B, QT interval showed non-significant ($p$> 0.05) changes at all intervals except at 10 min where significant ($p$<0.05) decrease was recorded after drug administration from the base values.

### *T wave amplitude*

In groups A and B, non-significant ($p$> 0.05) decrease in T wave amplitude at 10 min followed by non-significant ($p$>0.05) increase at 20 min to 60 min was registered after drug administration from their respective baseline values.

## Discussion

The decrease in the level of Hb can be due to the pooling of fluid from the extravascular compartment to the intravascular compartment in order to maintain the cardiac output in animal.[5] It may also be due to the pooling of blood cells in spleen or other reservoirs or haemodilution in response to fluid therapy.[6]The decrease in PCV can occur due to pooling of circulating erythrocytes in spleen or other reservoirs due to decreased sympathetic stimulation or as a result of an inter-compartmental fluid shift in order to maintain normal cardiac output.[6] During general anaesthesia the spleen usually expands, a process that can cause erythrocyte sequestration and a lowering of the haematocrit and haemoglobin concentration. The decrease in TLC may also result from pooling of circulating blood cells in spleen or other reservoirs secondary to decreased sympathetic activity in dogs.[7]As the present study was designed in clinical cases of canine orthopaedic patients, a significant stress was expected in these animals. Stress leads to adrenocortical stimulation and subsequent effects of glucocorticoids on circulating neutrophils.[7]

The decrease in PUN up to 60 min interval might be due to the continuous infusion of fluid that might have kept the kidney functions normal. The increase in PUN that occurs after administration of anaesthetics may be due to the effect of drugs on renal blood flow, changes in cardiovascular and neuroendocrine activity, which

**Table 3** Mean±SE values of various ECG indices in groups A and B at different intervals

| Parameter | Group | Interval (minutes) | | | | | |
|---|---|---|---|---|---|---|---|
| | | 0 | 10 | 20 | 30 | 45 | 60 |
| $P_{amp}$ (mV) | A | 0.22±0.03 | $0.27^{b}$±0.13 | 0.22±0.03 | $0.32^{*b}$±0.03 | $0.33^{b}$±0.05 | 0.28*±0.03 |
| | B | 0.20±0.00 | $0.18^{a}$±0.01 | 0.22*±0.11 | $0.26^{ab}$±0.02 | $0.21^{a}$±0.01 | $0.22^{ab}$±0.02 |
| $P_{dur}$ (sec) | A | 0.04±0.00 | 0.04±0.00 | 0.04±0.01 | 0.04±0.00 | 0.04±0.00 | 0.04±0.00 |
| | B | 0.04±0.00 | 0.04±0.00 | 0.04±0.00 | 0.04±0.00 | 0.04±0.00 | 0.04±0.00 |
| $QRS_{amp}$(mV) | A | 1.60±0.27 | $1.67^{b}$±0.35 | 1.62±0.32 | 1.62±0.27 | $1.57^{ab}$±0.27 | $1.72^{b}$±0.32 |
| | B | 1.73±0.21 | $1.77^{b}$±0.06 | 1.60±0.19 | 1.62±0.23 | $1.77^{b}$±0.23 | $1.62^{ab}$±0.06 |
| $QRS_{dur}$ (sec) | A | 0.06±0.11 | 0.06±0.00 | 0.07±0.00 | 0.06±0.00 | 0.06±0.00 | 0.06±0.00 |
| | B | 0.06±0.11 | 0.06±0.00 | 0.06±0.00 | 0.06±0.00 | 0.06±0.00 | 0.06±0.00 |
| PR (sec) | A | $0.09^{b}$±0.00 | $0.08^{b}$±0.00 | $0.08^{ab}$±0.00 | $0.08^{a}$±0.01 | $0.08^{a}$±0.01 | $0.08^{a}$±0.01 |
| | B | $0.10^{b}$±0.01 | $0.08^{b}$±0.01 | $0.09^{ab}$±0.02 | $0.09^{a}$±0.02 | $0.09^{a}$±0.01 | $0.09^{a}$±0.01 |
| QT (sec) | A | 0.19±0.01 | 0.18±0.01 | $0.17^{*}$±0.01 | 0.17±0.01 | 0.19±0.03 | 0.18±0.03 |
| | B | 0.19±0.00 | 0.18*±0.00 | 0.18±0.00 | 0.18±0.01 | 0.22±0.01 | 0.20±0.01 |
| $T_{amp}$ (mV) | A | $0.20^{a}$±0.04 | 0.18±0.03 | 0.48±0.31 | 0.42±0.26 | 0.38±0.17 | 0.34±0.13 |
| | B | $0.19^{a}$±0.04 | 0.16±0.02 | 0.19±0.01 | 0.20±0.03 | 0.19±0.03 | 0.18±0.03 |

*Significantly different from base value (P<0.05); Values with different alphabets differ significantly at respective intervals (P<0.05)

may affect renal functions. Plasma creatinine showed a significant increase in both groups. The increase in plasma creatinine and urea nitrogen values might be attributed to the temporary inhibitory effects of these anaesthetic drugs on the renal blood flow, which in turn might have caused a rise in plasma creatinine and plasma urea nitrogen level as suggested by Kinjavdekar *et al.*[8] Increased hepatic urea production from amino acid degradation could also account for the observed increase in plasma urea nitrogen values.[9]Since the present study was done on the clinical cases of orthopaedic affections with a lot of soft tissue injury, the animals were already under severe stress which might have resulted in the development of hyperglycemia at time zero during the presentation of the case. Surgical manipulation of the fracture added to the anaesthetic stress might also have contributed to the increased glucose level in these animals. Relaxation of all body muscles during anaesthesia may also lower the utilization of glucose at tissue level leading to hyperglycemia.[10] It has been reported that thiopentone has no effect on blood glucose.[11]Increase in plasma cortisol level may probably reflect the stress response as a result of struggling by the animals during restraining for intravenous administration of drugs. It is well known that cortisol is a stress hormone and its increased level indicates that the animals presented were in a state of stress due to a lot of bone and soft tissue injury. The increase in plasma glucose values is a good indicator along with the rise in cortisol that these animals were under severe stress. The values of plasma cortisol also increased during surgery as a result of surgical and anaesthetic stress was also reported in dogs.[12] The overall observation on blood biochemical parameter suggests that the alteration seen in different parameters were the outcome of general stress (anaesthetic and surgical) produced during the study as the changes were transient. Luna *et al* reported an increase in cortisol level during

thiopental-halothane anaesthesia.[13] Mirakhur *et al* observed a non significant progressive increase in plasma cortisol levels during thiopental anaesthesia.[14]As the drugs used in the present study have no direct action on the pancreatic β cells, the probable reason for the increase of insulin can be a homeostatic response to the cortisol-induced hyperglycemia in these animals. The net effect of high plasma cortisol and high plasma insulin resulted in maintenance of plasma glucose levels slightly higher than baseline values in the present study. The rate of clearance of circulating insulin in thiopentone anaesthetized dogs was less than in conscious control dogs, which suggests that thiopentone depresses plasma insulin level clearance by the body tissue is also in agreement with the present study.[15]

The use of atropine as pre-anaesthetic might have raised the atrial contraction leading to increased P wave amplitude. PR interval did not show any significant changes in all the groups. P-R interval reflects conduction of excitation from atria to ventricles, thus its length is closely related to heart rate. Increase in the heart rate in the animals in the present study might have been responsible for decreased PR interval at the respective times from their baseline values and respective groups from the other groups.[16] Since vecuronium has a good cardiovascular stability that might be the reason for the similar P wave and PR interval characteristics of the two groups. It was concluded in an earlier study that the length of QRS interval in dogs both in the initial state as well as in the course of premedication and general anaesthesia very much depended on the breed factor.[17] T-wave amplitude showed non-significant changes in both the groups at all time intervals. Diphasic and inverted T-waves occurred occasionally in some animals. The anaesthetic drugs used in this study did not change the duration of the T-wave and the amplitude of the T and R-waves, indicating that these drugs had no influence on the ventricular depolarization time as well as ventricular repolarization and ventricular enlargement.[16] The diagnostic value of T-wave changes in dogs is very limited in comparison with humans, as T-wave morphology is highly variable in animals.[18] Because of the numerous sources of inaccuracy with regard to QT measurement, it is difficult to evaluate the clinical and biological significance of minor QT changes, even when they are statistically significant.[19]Corrected QT (QTC) for heart rate at the intervals of a significant decrease in the present study explains the minimal effects of drugs on the QT interval.[20] Overall ECG was normal in all the groups and significance cannot be attached to some of the changes in time and voltage parameters of ECG. Wandering sinus pacemaker is a frequent normal finding in the dogs.[20] Diphasic T-waves in the animal correlated with intraoperative hypokalemia.[20] There is an inverse relationship between QT interval and heart rate.[21] In the present study thiopentone alone or thiopentone-vecuronium combination provide haematological, biochemical and electrocardiographic stability and thus may be considered safe for dogs.

## Conflict of Interest

None Declared

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