



## The effect of intravenous administration of propofol, thiopental, or propofol plus thiopental mixture in dogs undergoing experimentally liver insufficiency

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### ABSTRACT

The present study was aimed to evaluate anesthetic properties, clinic-physiological and hemato-biochemical effects of propofol alone, thiopental alone or propofol/thiopental mixture in dogs with experimental liver insufficiency. For this purpose, 9 apparently healthy male dogs exposure to electrocauterization to induce liver insufficiency model. The dogs were randomly divided into three groups; each group consists of three dogs. All dogs were premedicated with Xylazine Hcl (1mg/kg bwt/i.m). The induction of general anesthesia was done via i/v injection of 6 mg/kg bwt Propofol (group A); 5mg/kg bwt Thiopental (group B) and 3 mg/kg Propofol + 2.5 mg/kg Thiopental mixture (group C). Blood samples were collected from the three groups at 15mins before anesthesia induction then at 15, 30 and 45 minutes after treatments for both clinico-physiological and hemato-biochemical evaluations. A mild alteration in some physiological parameters and hemato-biochemical values was observed after anesthesia induction in all groups, but it still safe induce general anesthesia in dogs affected with liver insufficiency. However, Propofol /Thiopental mixture was induced a rapid, smooth induction and a longer duration of anesthesia with complete muscle relaxation which is suitable for all most surgical operations.

**Keywords:** Thiopental; Propofol; Propofol/Thiopental mixture; Liver Insufficiency; Dogs

### 1. Introduction

Thiopental, propofol, and ketamine are injectable general anesthetic agents used for induction of anesthesia in the healthy dog, also it may be administered in combination with diazepam to reduce the quantity needed and improve the quality of induction (McClune et al., 1992). Propofol /thiopental mixture showed benefits of reduced pain on injection, stability, reduced support of bacterial growth. Moreover, the mixture induces rapid smooth anesthesia, and absence of effect upon recovery profile (Pranker and Jones, 1996).

Propofol is an exclusive non-barbiturate, non- steroid, short-acting general intravenous anesthetic agent and may cause hypotension and apnea. Propofol is often chosen for patients with hepatopathy and for those where rapid recovery is desirable (Stoelting, 1999). Using ketamine or propofol alone has a shorter duration than their combination. Anesthetic duration of propofol may be improved when it combined with premedication like diazepam which is a well-known benzodiazepine derivative used in various animal species. It was stated to have a minimum effect on the respiratory system, heart rate, and rectal temperature. Also, it expected to cause good muscle relaxation and may be used to control

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convulsions. Still, studies on this combination are rare (Suresha et al., 2012).

No single anesthetic agent provides all of the components of general anesthesia without affecting some vital organ functions. Therefore, a multiple drug technique (balanced anesthesia) is exploited to reduce sensory, motor, sympathetic and parasympathetic reflex activities, and to diminish individual components of the anesthetic state (Potliya et al., 2015). The present study was aimed to evaluate anesthetic properties, clinic-physiological and hemato-biochemical effects of propofol alone, thiopental alone or propofol plus thiopental mixture on dogs with experimental liver insufficiency.

### 2. Material and methods

#### 2.1. Animals

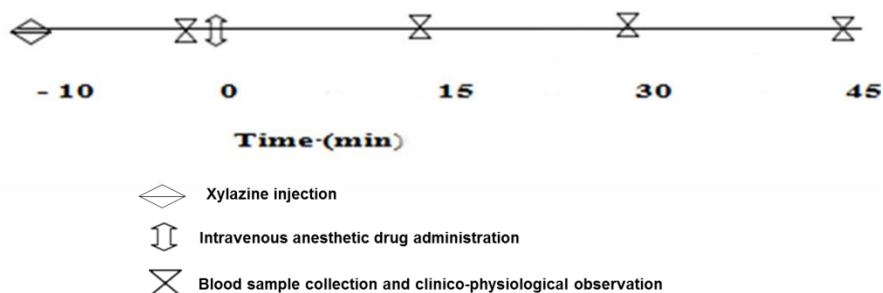
Nine apparently healthy adult male dogs with mean weights of (25 ± 5) kg and mean age of (10 ± 5) months- were used in the current study.

#### 2.2. Study design

The dogs were divided randomly into three groups; each group consists of three dogs. All dogs in each group were premeditated with the injection of Xylazine HCl (Xyla- Ject, Adwia Co., 10th Ramadan City, Egypt.) at the dose of 1mg/kg bwt, i/m injection (Muir et al., 1977). All dogs used in two main experimental groups: The first main experiment group contains 9 apparently healthy dogs for exposure to electro-coagulation of hepatic parenchyma by using diathermy directly on liver tissue to induce elevation of liver enzyme for further investigation of the anesthetic effect of Propofol, Thiopental sodium or Propofol + Thiopental mixture and evaluations both clinic-physiological and blood parameters values. The second main experimental groups (nine dogs) were subdivided into 3 groups; each group contains three dogs.

Experiment (I), Diathermy for induction of liver insufficiency, nine dogs were exposure to diathermy ten minutes after injection of the Xylazine Hcl following by intravenous injection of Thiopental sodium in a dose of 5 mg/kg bwt as a general anesthetic. The dog was turned into dorsal recumbency and the abdominal area prepared for surgery, five minutes after the intravenous injection of Thiopental sodium, an approximately 7cm long incision was done in the skin, muscle and peritoneum till reach to the liver. The incision was made under the costal arch at right side above the liver. After that a manual detaching of the liver lobes from surrounding organs has occurred. Monopolar diathermy was adjusted at 90°C to induce electrocauterization to three lobes of liver at different three points to obtained model dogs with experimentally liver insufficiency. Finally, the liver lobes were repositioning again under the ribs with usage of penicillin powder, then the muscle layers were sutured using simple continuous suture pattern with absorbable suture material(vicryl) of one size. The skin was sutured with horizontal mattress suture pattern using a non-absorbable suture material (silk, no.1) after 48hr from surgery blood sample was taken to analyze liver enzyme (ALT).

Experiment (II), The main experiment, the second main experimental groups (nine dogs) were subdivided into 3 groups; each group contains three dogs.



**Figure 1:** Showing the time of administration of pre-anesthetic and general anesthetic drug in addition to blood sample collection and clinico-physiological observations (heart rate, respiratory rate, temperature) time

**Table 1.** Values of induction and duration after intravenous injection of propofol, thiopental or the combination of propofol/ thiopental

Treatment	Onset/ sec	Duration/ min
Propofol	28.33±1.67	45.33±0.88
Thiopental	160±20.00	56.67±7.26
Propofol/ thiopental mixture	7.33±1.45	101.67±11.67

**Table 2.** Effect of propofol, thiopental or the combination of propofol/ thiopental on heart rate, respiratory rate, and temperature before and after treatments

Treatment	Time	Heart rate	Respiratory rate	Temperature
Propofol	Before treatment by 0 min	46.33 ±0.84 min	11.33 ±1.67 min	39.1 ±0.65 min
	After treatment by 15 min	48.67 ±4.1min	9 ±2.08 min	39.53 ±0.64 min
	After treatment by 30 min	49 ± 6.66 min	9.33 ±2.03 min	39.97 ±0.61 min
	After treatment by 45 min	50.67 ±6.39min	10.33 ±2.03 min	40.07 ±0.58 min
Thiopental	Before treatment by 0 min	44.00 ±8.72min	13.67 ±0.67 min	36.93±3.07 min
	After treatment by 15 min	39.00 ±9.54 min	11.33 ±0.33 min	39.3 ±0.53 min
	After treatment by 30 min	40.33 ± 9.53min	14.33 ±0.33 min	39.73 ±0.75 min
	After treatment by 45 min	41.67 ±9.82 min	15.67 ±0.33 min	39.53±0.52 min
Propofol/ Thiopental mixture	Before treatment by 0 min	60.67 ±8.71 min	17.00±1.00 min	39.33 ±0.09 min
	After treatment by 15 min	50.67 ±1.76 min	16.67 ±1.45 min	39.27 ±0.09 min
	After treatment by 30 min	56.33 ± 6.77 min	16.67 ±1.45 min	39.47 ±0.23 min
	After treatment by 45 min	59.33 ± 7.26 min	18.67 ±2.91 min	39.60±0.10 min

**Table 3.** Effect of propofol, thiopental or the combination of propofol/ thiopental on ALT, AST, total protein, albumin, and Glucose before and after treatment.

Treatment	Time	ALT	AST	Total protein	Albumin	Glucose
Propofol	Before treatment by 0 min	116.4±29.1	349.2±100.81	8.43 ±1.12	3.28 ±0.48	170 ±22.38
	After treatment by 15min	116.4±29.1	349.2±100.81	8.29 ±1.1	3.11 ±0.5	191.56±25.71
	After treatment by 30 min	174.00 ±0.0	261.9 ±87.3	8.44 ±0.49	2.81 ±0.21	251.88±51.78
	After treatment by 45 min	223.8±63.18	291 ±76.99	8.87 ±1.5	2.39 ±0.14	303.23 ±58.6
Thiopental	Before treatment by 0 min	181±84.24	241.27±54.46	10.6 ±1.55	5.14 ±1.27	226.52±32.27
	After treatment by 15 min	104.76±35.28	291 ±116.4	9.54 ±0.87	4.04 ±1.04	364.26 ±8.58
	After treatment by 30 min	133.83±64.03	320.1 ±76.99	9.57 ±1.33	3.75 ±0.32	374.88±19.41
	After treatment by 45 min	317.19±192.61	320.1 ±76.99	8.42 ±0.47	5.13 ±1.85	284.34±47.89
Propofol /Thiopental mixture	Before treatment by 0 min	145.5±29.1	261.9±100.81	8.22±0.71	2.5 ±0.27	337.72±103.35
	After treatment by 15 min	116.4±29.1	232.8 ±58.2	8.48±0.97	3.11±0.19	350.8 ±109.2
	After treatment by 30 min	116.4±29.1	203.7 ±29.1	7.45±0.27	3.06 ±0.32	133.74±23.57
	After treatment by 45 min	145.5±58.2	159.6 ±38.16	6.68±0.65	2.99 ±0.79	228.11 ±22.49

Group (A): After elevation of liver enzyme 3 dogs were injected intramuscularly with xylazine HCL in a dose of 1 mg/kg bwt, followed by Propofol in a dose of 6 mg/kg bwt., 10 min later by i/v route.

Group (B): After elevation of liver enzyme, 3 dogs were injected intramuscularly with xylazine HCL in a dose of 1 mg /kg bwt, followed by Thiopental sodium in a dose of 5 mg/ kg bwt., 10 min later by the same route.

Group (C): After elevation of liver enzyme, 3 dogs were injected intramuscularly with Xylazine HCL in a dose of 1 mg/kg bwt, followed by Propofol in a dose of 3 mg/kg bwt plus Thiopental sodium in a dose of 2.5mg / kg bwt.in one syringe, 10 min later by i/v route.

### 2.3. Animals preparation for anesthesia

All animals fasted for 24 hours and water was withheld 12 hours prior to surgery (parenchyma electrocoagulation of the liver) Diathermy while all dogs fasted for 12 hours before anesthesia with water ad libitum. The area over cephalic vein was clipped and shaved with manual shaver and use betadine as an antiseptic solution to be ready for administration of the drugs and blood samples collection. Dose calculation was calculated according to animal weight and preliminary study on the drug.

### 2.4. Assessment of anesthetic parameters

The anesthetic effects of the three protocols were evaluated through determining the onset of anesthesia (time from induction till loss of sensation and body reflexes and anesthesia duration (time from loss of sensation and regaining the sensation and body reflexes). Also, the absence and regaining of certain body reflexes were observed as skin reflex, palpebral reflex, and anal reflex. Evaluation of recovery depended observing the return of reflexes and recording Time to first head lifting. Moreover, dogs are observed for any behavioral changes, for example, hypersalivation, neurologic signs, vomiting, and urination.

### 2.5. Blood sample collection

Venous blood samples were collected in vials containing EDTA, for hematological determination of WBCs, RBCs, Hemoglobin concentration (HB %) and Platelets (PLT) 0 minutes before anesthesia induction, at 15, 30 and 45 min after drug administration. Part of blood was collected in plain tubes, for detection of the level of ALT, AST, total protein, albumin, and glucose (Fig. 1).

### 2.6. Clinico-physiological observations

The clinical observations of the following parameters were recorded at 15min before and 15, 30 and 45 min after anesthesia induction. The heart rate was measured as beats/min via auscultation (Ko et al., 2006). Respiratory rate (RR), measured by observing the movement of the thoracic wall motion per minute (Lemke et al., 2002). Rectal temperature measured with a digital thermometer (Medlink, Hamburg, Germany).

### 2.7. Statistical analysis

The data for parametric observations such as heart rate, respiratory rate, and rectal temperature were analyzed using a one-way analysis of variance (ANOVA) for comparison of means between the groups at corresponding intervals. The data were presented as the mean  $\pm$  SD. Significance was accepted at  $p < 0.05$ .

## 3. Results

### 3.1. General anesthetic effects

The determination anesthetic effects depended on three parameters include (onset of anesthesia or quality of induction, duration, and recovery).

### 3.2. Onset of anesthesia

A significant difference was observed in the onset and duration of anesthesia within the three groups. The mixture of Propofol and Thiopental group (C) showed the most rapid and smooth onset of action ( $7.33 \pm 1.45$ sec) while Thiopental group had the slowest onset of action ( $160 \pm 20.00$ sec) and the onset of anesthesia was quicker in Propofol group (A) ( $28.33 \pm 1.67$ sec) than Thiopental group (C) ( $160 \pm 20.00$ sec) as in table (1).

### 3.4. Duration of anesthesia

Regarding the duration propofol /thiopental mixture (C) has the longest duration A ( $101.67 \pm 11.67$ min) while Propofol (A) has the shortest duration ( $45.33 \pm 0.88$ ), also It was observed that Thiopental (B) ( $56.67 \pm 7.26$  min) has a longer duration than Propofol ( $45.33 \pm 0.88$ ) as in table (1).

### 3.5. Recovery

The recovery in all groups was smooth; however, convulsions and urination were observed during the recovery in dogs received propofol. the complete recovery was recorded by observing the time of first sternal recumbency, head lifting and standing so dogs received propofol/thiopental has the longest recovery time while dogs in the propofol group have the shortest recovery time.

### 3.6. Clinico-physiological findings (Heart rate, Respiratory rate, and Rectal temperature)

A significant increase in rectal temperature was observed in thiopental group while a non-significant change in rectal temperature was observed in propofol and mixture group. Regarding respiration rate, administration of propofol lead to a significant decrease but return to baseline. Also, there was a fluctuation in the respiratory rate in the thiopental group and propofol/thiopental group but still above the baseline. Concerning the heart rate, it showed a significant increase in propofol. But in the thiopental group, there was a fluctuation in heart rate but still above the baseline, while fluctuation in heart rate was observed following Propofol/Thiopental mixture administration as in Table (2)

### 3.7. Biochemical findings (ALT and AST, total protein, albumin, and Glucose)

There was fluctuation of the ALT level was observed in the thiopental group and in propofol /thiopental mixture group. Concerning propofol was observed the value constant from injection till 15 minutes then start increase until the end of the experiment. AST level a significant decrease was observed in the propofol/thiopental group throughout the experiment. There was significant increase in AST after thiopental mixture administration until the end of experiment. However, a fluctuation was observed in the Propofol group. A significant increase was observed in glucose levels throughout the experiment in propofol group. However, a fluctuation was observed in thiopental and in propofol /thiopental mixture group. there was fluctuation in total protein level was recorded in thiopental group while there was a decrease in Propofol then increase until the end of experiment as regarded to mixture group there was increase in total protein value then decrease till the end of experiment. Albumin showed non-significant decrease at 15 minutes after intravenous injection of propofol and thiopental until reached 45 minutes, but in the case of propofol /thiopental mixture, we noticed non-significant increase at 15 minutes and start to decrease again until reached around the baseline as in table (3).

### 3.7. Hematological findings (WBCs, RBCs, Hb%, and platelets)

A significant decrease in hemoglobin Hb % was observed in propofol /thiopental mixture but return to baseline. While in the propofol group found a significant increase then decrease on the opposite side thiopental group there was a significant decrease at 15 minutes and continued to decrease until the end of the experiment. however red blood cells count RBCs showed non-significant decrease in propofol/thiopental mixture and thiopental group but at propofol group observed that there was significant increase at the beginning then increase again to reach around baseline .as regarded to WBCs There was significant decrease until the end of experiment at Thiopental group and propofol /thiopental mixture but at propofol group there was significant increase at the beginning of propofol administration after that it began to decrease till reached to baseline. There was a fluctuation in platelets count in thiopental and propofol /Thiopental mixture although there was significant decrease in PLT count till the end of experiment at propofol group (Table 3).

## 4. Discussion

Recent anesthetic practices recommend combinations of drugs. This practice is known as balanced anesthesia in which multiple drugs are used in low dosage as each drug is used for a specific purpose. The main purpose is to take advantage of the required characteristics of selected drugs while reducing their ability for undesirable depression of homeostatic mechanisms (Riviere and Papic, 2009).

In this study, the anesthetic and the clinico- physiological effects of intravenous administration of Propofol alone and Thiopental alone and Propofol /Thiopental mixture in addition to hemato-biochemical findings were evaluated. In the present study, the onset of anesthesia induction in three groups was rapid and smooth, however, the dogs received Propofol Thiopental showed the quickest onset of anesthesia while dogs received Thiopental showed the slowest onset of anesthesia. Also, it was observed that the onset of anesthesia induction in dogs received Propofol was quicker than dogs received Thiopental. The current study showed that Propofol/Thiopental combination resulted in the longest anesthesia duration, the current study is compatible with Muhammad et al. (2009) who reported that propofol and thiopental combination induction was quicker than dog received propofol alone or thiopental alone and reduce the dose of propofol required for the induction of anesthesia.

Our findings are incompatible with ko et al (1999) who found that a combination of propofol and Thiopental induced anesthesia of similar quality to propofol or thiopental alone and recovery profile were similar to those of propofol and superior to those of thiopental. The findings of the current study may differ due to the breed and dose difference. A significant increase in heart rate was observed in the Propofol group. This finding is similar to the result of Jolliffe et al. (2007) who found that Induction of anesthesia with Propofol in dogs was associated with a mild increase in pulse rate and Martinez-Taboada and Leece (2014) who observed that ketofol administration was associated with a greater

increase in PR. the increase in heart rate may be due to sympathetic stimulation Agrawal et al. (2012). In contrast, bradycardia was observed after intravenous injection of Propofol. Regarding to the respiratory rate a significant decrease was observed after Propofol administration then returned to baseline while it showed a significant increase in Propofol-ketamine group and Propofol less than 50 minutes Hug et al. (1993), Tramer et al. (1997) and Fanton et al. (2000) however there was a significant decrease in heart rate then increase again and remain in increase but with low value less than baseline (Bradycardia) these results are similar to that reported by Duggel and Russell (2003) found that Thiopental cardio stable and cause less maternal bradycardia and hypotension, moreover significant decrease in heart rate after

Administration the mixture between Propofol and Thiopental then began in increase again till return to baseline in the same time Shaaban et al. (2018) proved that Propofol and Thiopental mixture caused a fluctuation in heart rate along the period of anesthesia, On the other side Jolliffe et al. (2007) mentioned that Propofol Thiopental mixture cause significant increase in heart rate in normal patient. The liver diseased dog, which injected with Propofol showed a significant decrease in respiratory rate then increased slightly till it reached the normal rate at 45 minutes.

These results are agreed to that found by Blouin et al. (1993) who showed respiratory depression followed Propofol administration due to the decreases in the invitatory response to carbon dioxide CO<sub>2</sub> and arterial hypoxemia due to effect on central chemoreceptors also the level of respiration depression was related to Propofol concentration in the central nervous system CNS.

At the same time, Jonsson et al. (2005) mentioned that propofol results in hypoventilation by directly depressing central inspiratory drive and the respiratory response to the partial pressure of carbon dioxide in arterial blood Pa CO<sub>2</sub>. Also, Muhamed et al. (2009) who noticed that there was a significant decrease in respiratory rate after administration of two different doses of Propofol moreover Kotani et al. (2008) and Kelci (2014) reported that Propofol administration lead to respiratory depression but slow induction minimize the respiratory effect on the drug Sulli et al. (2008).

Contrarily Hafez (2017) found that there was a significant increase in respiratory rate following Propofol administration, then decreased and return to the baseline at the end of the experiment. As regarded in the present study, there was a significant decrease in respiratory rate after intravenous injection of Thiopental sodium then suddenly increase till the end of the experiment. In contrast, laryngeal spasm and respiratory depression are the most adverse effect of Thiopental sodium administration (Pait et al. 1984). Moreover, experimental liver diseased dogs treated with mixture between Propofol and Thiopental showed significant decrease in respiratory rate, then suddenly increase till the end of experiment. While Shaaban et al. (2018) recorded that mixture of Propofol and Thiopental in normal dogs didn't induce any significant changes in respiratory rate along the period of anesthesia. Lastly the Rectal Temperature value of the experimental liver insufficiency showing non-significant changes when the animal administrated with Propofol throughout the time of experiment. These results were agreed with that obtained by Hafez (2017) who reported that there were non-significant changes in rectal temperature after Propofol administration. On the opposite side Shaaban (2018) reported that an insignificant decrease in rectal temperature was observed after intravenous injection of Propofol in normal dogs.

In the group of thiopental sodium, when injected to the experimental dog. It was found that a significant increase in rectal temperature after 15 minutes and continued until the end of the experiment. While Muhammad et al. (2009). Observed that the body temperature decreased in dog after intravenous administration of Thiopental sodium. Concerning in the group of mixture between Propofol and Thiopental rectal temperature showed non-significant changes in all dogs and around its baseline values throughout the experiment. on the other hand, Shabaan (2018) concluded that a significant decrease in rectal temperature followed anesthetic induction in the combination of two drugs according to Zhang et al. (2012) the decrease in rectal temperature is related to the generalized sedation, muscle relaxation and the decrease in metabolic rate. This study showed a change in Hb, RBCs, WBCs, and platelets count.

Also, our results showed a fluctuation in ALT in the propofol and thiopental group. The decrease hemato-biochemical parameters during anesthesia or sedation may be due to shifting of fluid from the extravascular compartment to the intravascular compartment (Zhang et al., 2012) at mixture group there was fluctuation in ALT and AST value this result agree with the result obtain by Shaaban et al. (2018) in normal dog. Zahir et al (1995) concluded that a fluctuation in ALT and AST after injection of propofol and diazepam may be due to the hepatotoxic effect of diazepam. The blood cell count was diminished due to multiple and

continued blood sampling, although the use of propofol was associated with greater decrease (Gronert et al., 1998), while glucose level showed a significant increase in the three groups that may be a response to stress (Singh, 2003), or as result of hyperglycemic effect of ketamine or xylazine as (Saha et al., 2005) but in propofol group glucose level increase till the end of experiment but in thiopental and mixture group start to decrease until the end of experiment.

### Conclusion

The anesthetic protocols of i/v injection of Propofol alone, Thiopental alone or Propofol /Thiopental mixture in dogs could be used for induction of general anesthesia, despite some mild changes in both physiological and biochemical parameters. Propofol/thiopental combination was showed the longest duration and smoothest induction and recovery, so it is a suitable general anesthetic protocol and advisable to be used in many surgical procedures of longer duration in dogs undergoing liver insufficiency.

### Competing Interests

The authors have no conflict of interest.

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