

EFFECT OF ORAL CLONIDINE PREMEDICATION ON INTRAVENOUS ANAESTHETICS

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ABSTRACT: OBJECTIVES: To study the effect of oral clonidine premedication on the induction doses of intravenous thiopentone sodium and propofol. **METHODS:** After ethical committee approval and informed consent, 120 ASA grade I and II patients were randomly allocated to four groups of 30 each. Group A received a placebo orally, 90 minutes before induction with thiopentone. Group B received clonidine 4µg/kg orally, 90 minutes before induction with thiopentone. Group C received a placebo orally, 90 minutes before induction with propofol. Group D received clonidine 4µg/kg orally, 90 minutes before induction with propofol. The patients were premedicated with Tab Diazepam 5 mg orally on the night before surgery. Inj. Glycopyrrolate 0.004 mg/kg IV was administered before starting anaesthesia. The patients were pre-oxygenated with 100% oxygen for 3 minutes and anaesthesia was induced with either thiopentone sodium 2.5% or propofol, slowly till loss of eyelash reflex was achieved. The dose of either thiopentone sodium or propofol required for induction of anaesthesia was noted. Inj. Succinylcholine 1.5 mg/kg was injected intravenously to facilitate tracheal intubation and after intubation anaesthesia was continued in the conventional manner. The heart rate and blood pressure were recorded throughout the procedure. **RESULTS:** The dose of thiopentone sodium required for induction was significantly lower by 21.3% in the group B (3.65±0.3 mg/kg) as compared with the control group A (4.64±0.35 mg/kg), effect size, d=2.02, p<0.001. The dose of propofol required for induction was significantly lower by 16.01% in the group D (1.73±0.08 mg/kg) as compared with the control group C (2.06±0.06 mg/kg), effect size, d=0.92, p=0.001. **CONCLUSION:** Oral clonidine premedication decreases the induction doses of both thiopentone sodium and propofol.

INTRODUCTION: Clonidine, a centrally acting alpha-2 receptor agonist, has attracted increasing interest as an adjunct to anaesthesia. A variety of beneficial effects before, during and after anaesthesia, such as sedation, suppression of intubation response, analgesia, decreased anaesthetic requirements, increased cardiovascular stability and improved outcome, have been attributed to clonidine.¹ The introduction of thiopentone sodium into clinical practice in 1934, marked the advent of intravenous anaesthesia, its property of producing peaceful sleep easily led to its rapid acceptance as one of the most commonly used intravenous induction agent. Propofol has several advantages like provision of rapid, smooth induction of anaesthesia and rapid recovery. However, an ideal intravenous induction agent is still eluding the anesthesiologists in spite of constant research. Many new adjuncts to intravenous induction of anaesthesia have been tried to improve the induction characteristics and to prevent the unwanted side effects of these agents.² The most widely used intravenous induction anaesthetics agents are thiopentone sodium and propofol. They have been reported to have a variety of effects on the central nervous system. This has led to a growing interest in studies investigating the interactions between them and other centrally acting drugs.

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The purpose of this study is to evaluate the hypnotic interaction between orally administered clonidine on the doses of the intravenous induction agents, thiopentone sodium and propofol.

METHODOLOGY: The present study was carried out on 120 patients of both sexes between the age groups of 18 to 50 years, admitted to hospitals attached to our Institute who were scheduled to undergo various elective surgical procedures under general anaesthesia during the period from November 2010 to March 2013. The personal and medical history was obtained by interview and in hospital inpatient sheet.

Inclusion criteria: Adult patients of either sex between 18 to 50 years of age posted for elective surgery. American Society of Anesthesiology (ASA) grade I and II.

Exclusion criteria:

- a. Patients with psychiatric disorders.
- b. Patients on any antihypertensive, antipsychotic medications.
- c. Patients with cardiac, respiratory, metabolic hepatic, renal, neurological disorders and gross malnutrition.
- d. Patients undergoing emergency surgeries.
- e. Allergy to sulpha group of drugs, egg lecithin, or soyabean oil.
- f. Pregnant and lactating mothers.

All procedures for this study were in accordance with the standards of the ethical committee in our institute and clearance was obtained from them. Informed consent was taken from the patient after explaining the procedure to them. A careful preanesthetic evaluation was done by taking history and by clinical examination. Weight, pulse rate, blood pressure, respiratory rate were noted.

A prospective placebo controlled double blind study consisting of 30 patients in each group A, B, C and D, for studying the effect of oral clonidine premedication on the induction dose thiopentone sodium and propofol was carried out. The patients were randomly allotted in the 4 groups and the control or a test drug was administered by a doctor not participating in this study. The patients were asked to stay nil orally for 6 hours before the start of the premedication. After administration of the drug or placebo, an intravenous line was started with Ringer Lactate at 2ml/kg/hr. The patients' heart rate, blood pressure, respiratory rate and oxygen saturation were monitored at regular intervals in the preinduction room. The haemodynamic parameters viz. heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were observed at five minute intervals during the induction of anaesthesia.

Group A received a placebo orally, 90 minutes before induction with thiopentone.

Group B received clonidine 4µg/kg orally, 90 minutes before induction with thiopentone.

Group C received a placebo orally, 90 minutes before induction with propofol.

Group D received clonidine 4µg/kg orally, 90 minutes before induction with propofol.

The patients were pre-oxygenated with 100% oxygen for three minutes. Anaesthesia was induced with injection Thiopentone sodium (2.5%) or Propofol (1%) accordingly, slowly till loss of eyelash reflex was noted by an anesthesiologists blinded (not a part of the study) to which group the

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patient was allocated to and the dose for induction recorded. Inj. Succinylcholine 1.5 mg/kg body weight was administered intravenously for facilitation of intubation.

Anaesthesia was maintained with oxygen, nitrous oxide and halothane. An opioid, Inj. Butorphanol 0.03mg/kg was administered for analgesia after intubation. Neuromuscular blockade was with Vecuronium 0.1 mg/kg and ventilation with Bain's circuit. The surgery was started 5 minutes after maintenance of anaesthesia.

The patient was monitored with ECG, pulse oximeter and NIBP throughout the procedure. The heart rate and blood pressure were recorded at the following intervals.

T1 – Baseline

T2 – Before induction

T3 – After induction

T4 – Immediately after intubation

T5 – 5 minutes after intubation

The mean arterial pressure was calculated at different stages according to the formula:

Mean arterial pressure = Diastolic pressure + 1/3rd pulse pressure.

The same monitoring was continued throughout the surgery at 5 minute intervals.

At the end of surgery, patient was given Inj. Neostigmine 0.05mg/kg along with Inj. Glycopyrrolate 0.01mg/kg intravenously to reverse the neuromuscular blockade. The patient was extubated after a satisfactory reversal and throat suction.

The patient was followed up postoperatively for any untoward effects at hourly interval till 9 hours after administration of clonidine.

STATISTICAL METHODS: The demographic data like age and weight were compared using one way analysis of the variance (ANOVA). The sex distributions in the different groups were compared using Chi square test. The mean values of doses of thiopentone and propofol given, the heart rate and blood pressure recordings were analyzed using the one way analysis of variance (ANOVA). When this test leads to the rejection of hypothesis of equality of means, then the Turkey's test was carried out for pair wise comparison. The tests were carried out at 5% level of significance, i.e. p value < 0.05 was taken as significant. Student t test (Independent) has been used to find the significance of difference of haemodynamic between the groups. Repeated measures ANOVA have been used to find the significance of haemodynamic over the study period. Effect size by Cohen is computed to find the effect of Clonidine on induction dose of Thiopentone and Propofol.

The Statistical software namely SPSS 11.0 and Systatic 8.0 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc.

RESULTS: The demographic data of various groups are depicted in Table 1.

It was observed that age in years, mean weigh and sex are comparable between the four groups and are not statistically significant (p>0.05). It is observed from table 2 that the reduction in the total dose of thiopentone is 23.96% in those who received clonidine premedication and is statistically significant. Also, a reduction of 21.3% in the dose of thiopentone per kg body weight was noted in the group that received clonidine.

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It is observed from table 2; the reduction in the total dose of propofol is 11.5% and is also statistically significant. Also, a reduction of 16.01% in the dose of propofol per kg body weight was noted in the group that received clonidine as compared to those who did not receive clonidine premedication.

As observed in fig 2 and 3, in both the groups, the basal and pre-induction heart rates were comparable and the difference between the groups was not statistically significant ($p>0.05$). After induction, the rise in the heart rate in both the groups were similar, and was found to be less in the group that received clonidine compared to the other group but there is no statistical significance ($p=0.676$). A statistically significant reduction of 6.76% in the heart rate was noted in the test group immediately after intubation. 5 minutes after intubation the heart rate was closer to the pre-induction value in both the groups.

The basal and pre induction systolic blood pressures were comparable in both the groups.

Just after intubation, there was a significant decrease in the systolic blood pressure in the group which received clonidine, as compared with the control group. A 15.79% decrease in SBP was noted in the test group as compared to the control, and is statistically significant.

The SBP returned to comparable levels in both the groups after 5 minutes after intubation.

The diastolic BP showed a similar behaviour as the systolic BP with the test as compared to the controls.

As observed in fig 4 and 5, the basal and pre induction mean arterial blood pressures are comparable in both the groups. Just after intubation, a statistically significant decrease in mean arterial blood pressure was noted in the test group as compared to the control.

The mean arterial blood pressure returned to comparable levels in both the groups after 5 minutes after intubation.

DISCUSSION: The α_2 agonists are assuming greater importance as anaesthetic adjuvant and analgesics. Their primary effect is sympatholytic. They reduce peripheral noradrenaline release by stimulation of prefunctional α_2 inhibitory adrenoceptors. They inhibit central neural transmission in the dorsal horn by presynaptic and postsynaptic mechanisms and directly in spinal pre-ganglionic sympathetic nerves. Traditionally, they have been used as antihypertensive drugs, but uses based on sedative, anxiolytic, and analgesic properties are being developed.^{3, 4} The interaction between various adjuncts to anaesthesia and the drugs used to induce general anaesthesia gains importance today as there is no ideal induction agent. Several drugs such as fentanyl and midazolam are often administered in conjunction with the commonly used induction agents, thiopentone and propofol. The pharmacodynamic profile of clonidine suggests that it may also be suitable for this purpose especially because it produces minimal respiratory depression.⁵ It is well known that clonidine decreases arterial blood pressure and heart rate by enhancing the parasympathetic nervous system activity and decreasing sympathetic nervous system activity at the brain stem sites.⁶ Clonidine premedication has also found to reduce the haemodynamic response to endotracheal intubation.⁷

From our study, we know that clonidine premedication greatly reduces the cost of the induction agents used for intravenous anaesthesia. The interaction between clonidine and various anaesthetic drugs has been studied by many workers. Nishina K et al, in their study on the effect of oral clonidine on the induction dose of thiamylal observed that the induction dose of thiamylal, a

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drug similar in characteristics to thiopentone, was 3.4 ± 0.9 mg/kg in those who received oral clonidine, 4 compared to 5.4 ± 0.9 mg/kg in the control group.⁸

Baskaran N et al observed that the dose of thiopentone required for induction was 5.5 ± 1.15 mg/kg in those who received clonidine $4 \mu\text{g}/\text{kg}$ orally, 90 minutes before induction, as compared to 4.15 ± 1.46 mg/kg (a reduction of 25%) in the control group.⁹

The present study done by us showed similar results as the dose of thiopentone required for induction in group B, those who received clonidine $4 \mu\text{g}/\text{kg}$ orally, 90 minutes before induction with thiopentone was 3.65 ± 0.3 mg/kg, as compared to 4.64 ± 0.34 mg/kg in group A, which received a placebo. A reduction of 21.3% in the dose of thiopentone per kg body weight was noted, which is significant.

Goyagi T et al, in their study on the effect of oral clonidine on the induction dose of propofol observed that the induction dose of propofol in those who received oral clonidine $5 \mu\text{g}/\text{kg}$ orally, 90 minutes before induction was 1.4 ± 0.3 mg/kg as compared to 1.9 ± 0.4 mg/kg in the control group. A reduction of 26.3% in the induction dose of propofol was noted. In another study by the same group, they found that oral clonidine; $5 \mu\text{g}/\text{kg}$ reduced the propofol requirements by 20% for LMA insertion.¹⁰

The present study done by us showed a reduction of 16.01% in the dose of propofol per kg body weight was noted. The reduced induction dose of propofol and thiopentone in the clonidine treated patients is considered as an additive hypnotic effect of clonidine. Although this effect may be solely due to a decrease in central noradrenergic transmission, the α_2 receptor itself may mediate an anaesthetic response. Maze M et al using molecular biologic techniques, they confirmed that the α_2 adrenergic C4 isoreceptor was the probable receptor that mediated the anesthetic response. They also established that the anaesthetic action of dexmedetomidine involved a pertussis toxin-sensitive G protein and a 4-aminopyridine-sensitive potassium channel.¹

There are other studies which studied the effects of clonidine on the anaesthetic requirements of intravenous anaesthesia, inhalation agents and analgesics. All these studies observed that premedication with clonidine reduced the anaesthetic requirements of these agents from 20% to 45%.

The changes in haemodynamic values were not the primary variables in our study. The attenuation of the cardiovascular response to intubation by oral clonidine premedication has been recognized by many studies.

Carabine et al observed an attenuated haemodynamic response to intubation in those who received clonidine premedication.¹¹ Dorman BH et al observed stable haemodynamic status when patients who were premedicated with clonidine for coronary artery bypass graft surgery.¹²

In our study it was noted that the rise in the heart rate was less in the clonidine premedicated groups after intubation as compared to the other two groups which did not receive clonidine.

The groups which received clonidine premedication were associated with significantly stable haemodynamic status after both induction and intubation compared with the control groups. These haemodynamic effects are similar to those observed by Carabine et al.

The present study confirms that the requirement of inducing agents is reduced when the patient has received oral clonidine premedication. Appropriate dosage adjustments in the induction doses of thiopentone and propofol have to be made when clonidine has been used for

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premedication. These results suggest that clonidine premedication, merely for reducing the dose of the induction agent may not be clinically relevant, although clonidine may provide other benefits, such as suppression of pressor response to intubation and better perioperative haemodynamic stability.

CONCLUSION: It can be concluded from the present study that when oral clonidine is given as premedication, the i.v. induction dose of thiopentone sodium and propofol is reduced and it should be carefully titrated against the patient's response rather than the conventional regime based on the patient's body weight. It was also associated with a reduced haemodynamic response to induction and intubation.

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Table 1: Basic characteristics of the study

Basic characteristics	Group A	Group B	Group C	Group D
Number	30	30	30	30
Age in years (Mean ± SD)	35.73±11.01	32.42±8.93	33.47±11.19	34.13±7.68
Sex	Male=46.7% Female=53.3%	Male=53.3% Female=46.7%	Male=53.3% Female=46.7%	Male=50.0% Female=50.0%
Weight (kg) (Mean ± SD)	58.20±8.43	56.00±8.18	57.97±7.49	61.07±8.99

Samples are age matched (P=0.618), sex matched (P>0.05), Weight matched (P=0.133)

Table 2: Effect of Clonidine dose on induction dose of Thiopentone and Propofol

Results are presented in Mean ± SD (Min-Max)

Effect of Clonidine	Thiopentone		Propofol	
	Without Clonidine	With Clonidine	Without Clonidine	With Clonidine
Number	30	30	30	30
Clonidine dose(µg)	-	228.33±31.30 (200-300)	-	248.33±42.51 (200-300)
Dose (mg)	268.3±30.2 (212.5-325.0)	204.0±32.5 (150-300)	119.0±14.3 (100-146)	105.3±15.3 (80-128)
Percentage reduction in the dose		23.96%		11.5%
Dose (mg/kg body weight)	4.64±0.35 (3.98-5.43)	3.65±0.30 (3.02-4.35)	2.06±0.06 (1.89-2.22)	1.73±0.08 (1.57-1.96)
Percentage reduction in the dose (mg/kg)		21.3%		16.01%
Cost (Rs)of Clonidine	-	1.59	-	1.74
Cost (Rs) of induction dose	25.75	19.58	107.10	94.77
Total cost (Rs)	25.75	21.17	107.10	96.51
Significance	Student t=7.942, P<0.001**		Student t=3.571, P=0.001**	
Effect size (d) of Clonidine on induction dose	2.02		0.92	

Figure 1a: Effect of Clonidine on Thiopentone

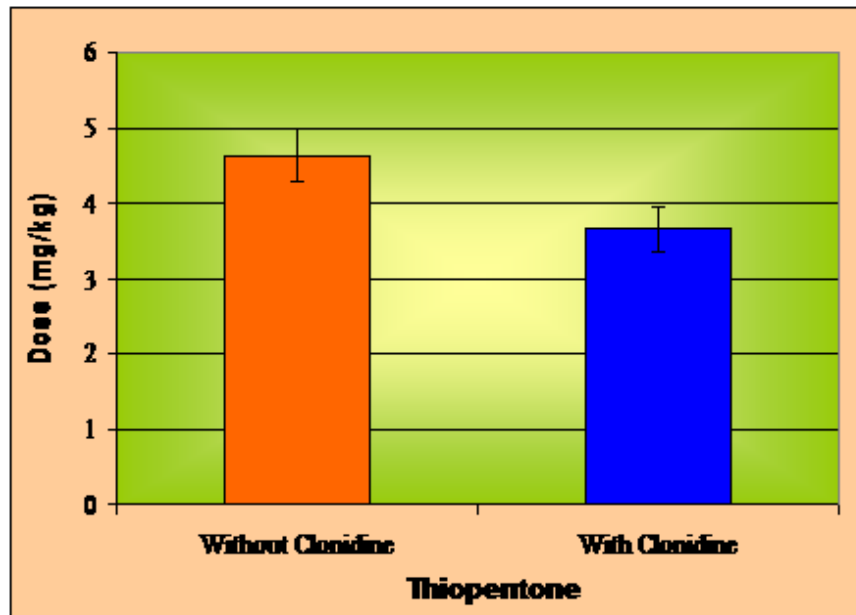


Figure 1b: Effect of Clonidine on Propofol

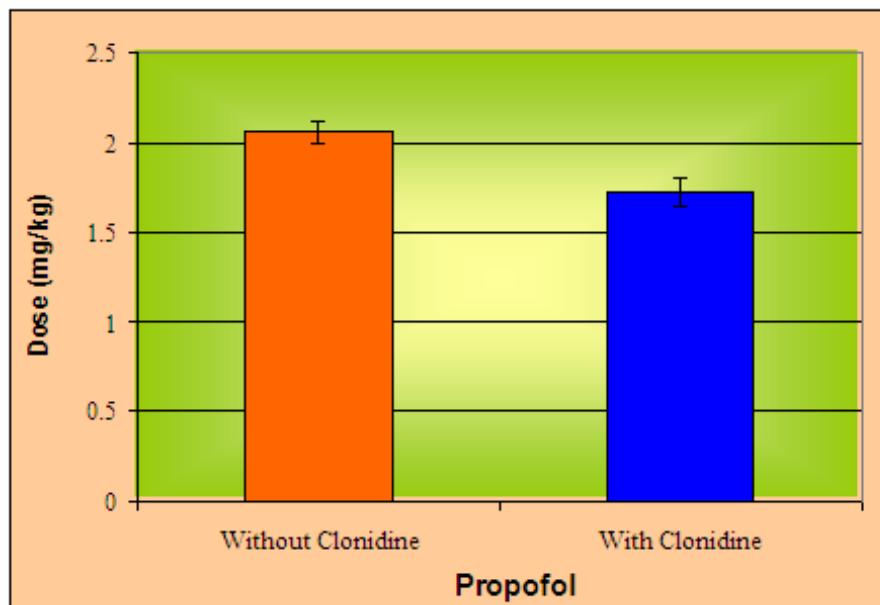


Fig 2. Comparison of Heart rate between Thiopentone Control and Test

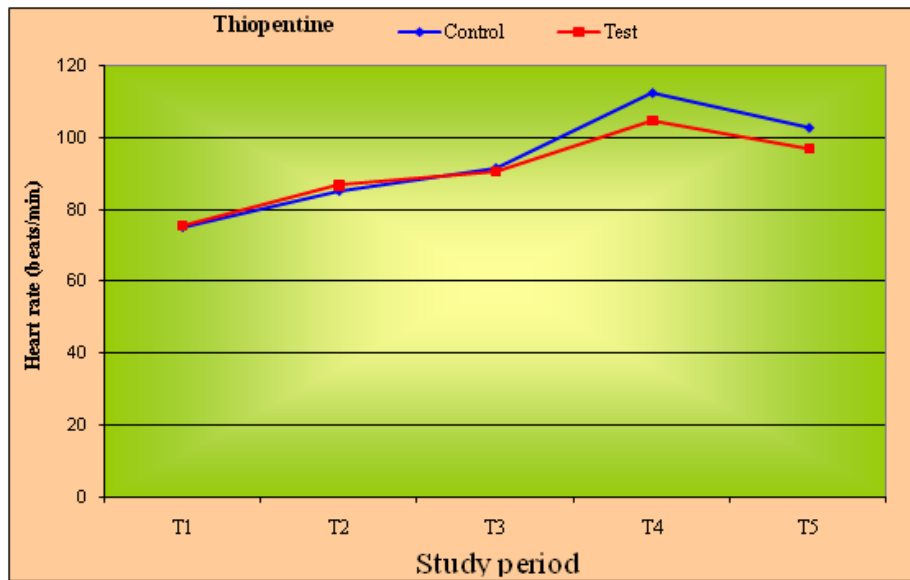
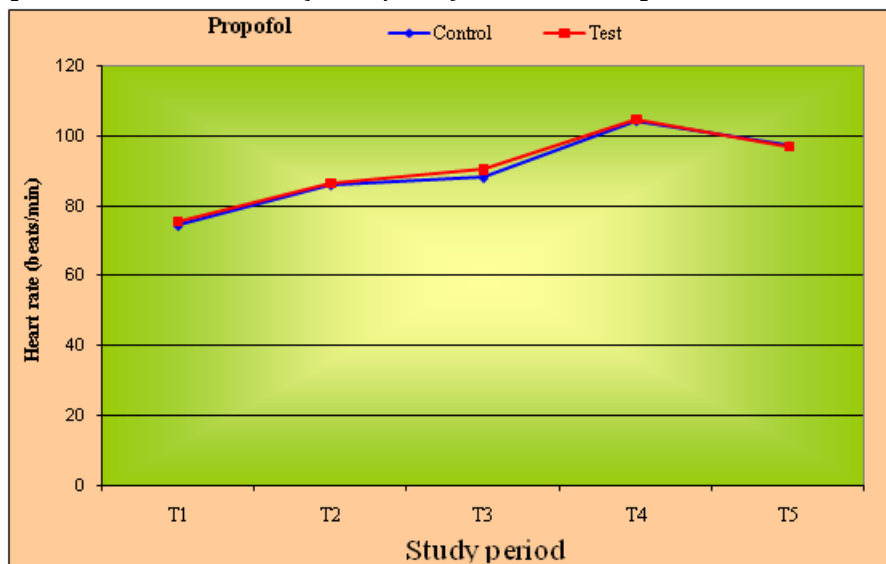


Figure 3: Comparison of Heart rate (beats/min) between Propofol Control and Test



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Figure 4: Comparison of MAP (mm Hg) between Thiopentone Control and Test

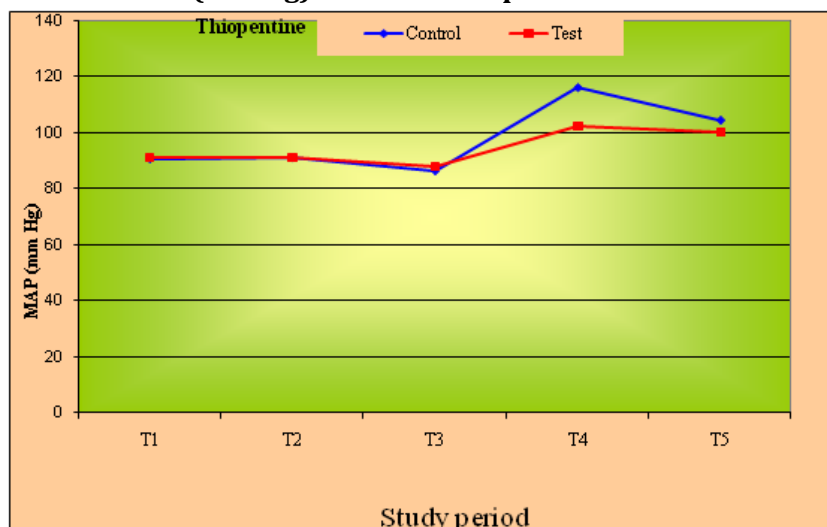
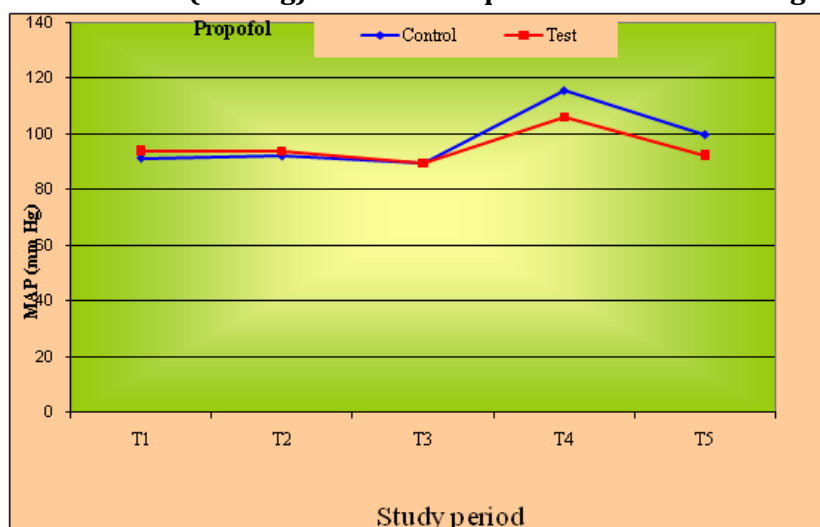


Figure 5: Comparison of MAP (mm Hg) between Propofol Control and Test groups



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