

COMPARISON OF THE EFFECT OF THIOPENTONE- MIDAZOLAM COMBINATION WITH THIOPENTONE FOR ANAESTHETIC INDUCTION

NIRANJAN KUMAR^{*}, ASHOK KUMAR^{**}

ABSTRACT

BACKGROUND: Induction is one of the essential phases of general anesthesia and is considered as the most critical part of the anesthesia process. The desired results that an ideal intravenous anesthetic drug might provide include a. hypnosis, b. amnesia, c. analgesia and d. muscle relaxation. Many studies were conducted using propofol and midazolam as co-induction agents and only few studies were conducted using thiopentone and midazolam as a combination. This study aimed at comparing the effectiveness of Thiopentone-midazolam combination as against thiopentone in a dose that is acceptably low and safe for the quality of induction.

MATERIAL AND METHOD: This study hypothesized that thiopentone-midazolam combination in a dose acceptably low and safe will be a better induction agent than thiopentone alone in terms of time taken for onset of sleep, hemodynamic stability. A prospective randomized, double-blind study was conducted in the patients, of Patna Medical College, India, in the year of 2010. 90 patients categorized into three groups of 30 each. Group T₄, T₃, and T₂, received injection thiopentone, midazolam intravenous.

RESULT: In this study, we had compared the time loss of verbal contact, loss of eyelash reflex and loss of movement on painful stimulus following induction of anaesthesia, the changes in oxygen saturation, heart rate (HR), blood pressure (BP) following induction of anaesthesia and endotracheal tube (ETT) insertion.

CONCLUSION: This study has proved that midazolam in a safe dose range reduces the dose of thiopentone for induction of anaesthesia.

KEYWORDS: Induction Agents, Intravenous Anaesthetic Drugs, Midazolam, Thiopentone, Thiopentone-Midazolam Combination.

^{*} Assistant Professor, Santosh Medical College and Hospital, Gaziabad, UP 201009 (formerly, Junior Resident, Patna Medical College and Hospital, Patna).

^{**} Head of the Department, Nalanda Medical College and Hospital, Patna (formerly, Professor and Head of Department, Patna Medical College and Hospital, Patna).

Correspondence E-mail Id: editor@eurekajournals.com

INTRODUCTION

Induction is one of the essential phases of general anaesthesia and it refers to the period between the initial administration of the anaesthetic agents and the loss of consciousness and it can be achieved by intravenous injection of induction agents, by the slow inhalation of anaesthetic vapour from a face mask, or a combination of both. These induction drugs are used to induce and maintain anaesthesia for longer procedures¹.

The Pharmacodynamic properties of these induction agents include a. high therapeutic ratio, b. minimal cardiovascular and respiratory effects, c. no adrenocortical suppression, and d. Safe to use in porphyria. Khan et.al (2014)² observes that despite their excellent safety record, the ideal i.v. anaesthetic agent does not yet exist, because all of these agents produce undesirable cardiorespiratory depression and hence these induction drugs may be used often together, so as to offer some or all of the desired pharmacological and physiological effect. Innovations in the area of Molecular Pharmacology and Neuropharmaceutics have shed light on the pathways and mechanism of action of anesthetic drugs on our nervous system. As defined by Paul et.al, (2010) anaesthesia is a clinical state where a myriad of behavioral endpoints are caused by a group of drugs that bear no physical resemblance to one another.³ Earlier practice of using single anesthetic drug as induction agent has been replaced by intravenous administration of combination of anesthetic drugs. Several Studies have revealed that the practice of combined anesthetic drug use may be safer than the use of only one or two drugs.⁴

OBJECTIVES

To compare the effectiveness of Sodium Thiopentone-Midazolam Hydrochloride combination with Sodium Thiopentone for the

quality of induction in patients scheduled for elective surgeries requiring general anaesthesia.

- To determine the time taken for the onset of sleep

HYPOTHESIS

The hypothesis of this study was that thiopentone-midazolam combination in a dose acceptably low and safe⁵ (thiopentone 3 mg/kg and midazolam 0.02 mg/kg) will be a better induction agent than thiopentone alone (Thiopentone 4 mg/kg) in terms of time taken for the onset of sleep, hemodynamic stability.

RESEARCH DESIGN AND METHODOLOGY

Type of Study: Comparative prospective randomized double-blind study.

Place of study: General operation theatre, Patna Medical College & Hospital.

Duration: 2 years from 2010 to 2012

Sample size: 90 patients categorized into three groups of 30 each. Group T₄, T₃, and T₂, received injection thiopentone, midazolam intravenous as described below. The cases were randomized according to non-probability sampling.

CRITERIA FOR SAMPLE SELECTION:

Inclusion criteria:

- ASA Physical Status I & II
- Both gender (Male/Female)
- Age 20-60 yrs. old years
- Elective surgeries requiring general anaesthesia

Exclusion criteria:

- Patients refusal

- Patients with known allergy to midazolam and barbiturates
- Asthmatic patient
- History of porphyria or psychiatric disorder

METHODOLOGY

Following Institutional Review Board (IRB) approval and written informed consent obtained from patients, 90 adult patients both male and female, scheduled for elective surgeries requiring general anaesthesia, meeting the inclusion criteria and not having any of the exclusion criteria, were taken for the study and were randomized into three groups.

- Group T₄ received inj. Normal Saline as 1st drug & inj. Thiopentone 4 mg/kg as 2nd drug
- Group T₃ received inj. Midazolam 0.02 mg/kg as 1st drug & inj. Thiopentone 3 mg/kg as 2nd drug.
- Group T₂ received inj. Midazolam 0.02 mg/kg as 1st drug & inj. Thiopentone 2 mg/kg as 2nd drug

Any deficiency in induction is supplemented by top up bolus of Thiopentone 25 mg.

DRUGS USED

1. Thiopentone sodium injection.
2. Midazolam injection (Vial)
3. Glycopyrrolate
4. Pentazocine lactate
5. Vecuronium Bromide injection.
6. Neostigmine methyl sulphate injection.
7. Ondansetron injection.
8. Emergency drugs.
9. Various intravenous fluids e.g normal saline, 5% dextrose, 5% dextrose in normal saline, Ringer's lactate.

FORMULATION OF THE STUDY DRUGS:

- 0.9% NaCl
- % Midazolam in 5 ml vial
- 2.5% Thiopentone in 0.9% NaCl (20 ml)

Composition of Midazolam I.P 5 ml vial, each ml contains:

- Midazolam B.P. 1.0 mg.
- Benzyl alcohol (as preservative) 1.0% v/v
- Water for injection q.s.

Composition of Thiopentone I.P. 0.5 g vial contains:

- Thiopentone sodium 0.5 gm.
- Sodium carbonate (anhydrous) 6.0%

Midazolam is diluted with normal saline to make it 0.2 mg/ml by diluting 4 mg midazolam to 20 ml. Thiopentone is made 2.5% by diluting 0.5 gm. vial with 20 ml normal saline.

Mixing of thiopentone sodium - an alkaline salt and midazolam hydrochloride - an acid salt, appears to result in precipitation of thiopentone, so drugs are loaded in different syringes and given one after other in different arm.

DATA COLLECTIONS AND ANALYSIS

Data was collected and recorded as per the Performa. Numerical variables like age, weight were compared by independent t- test and categorical variables like gender were compared by using chi- square test. Variables measured at different time intervals like HR, SBP, DBP, and MAP were compared by using paired t test. Statistical significance was accepted when $p < 0.05$. Results were presented as mean \pm SD.

OBSERVATIONS AND RESULTS

This study was a prospective randomized, double-blind study to compare sodium thiopentone- midazolam combination and sodium thiopentone alone for the quality of induction in patients scheduled for elective surgeries requiring general anaesthesia in Patna Medical College Hospital, Patna from 2010-2012.

Ninety adult patients both male and female, American Society of Anesthesiology grade ASA I & II, aged 20-60 years, were randomized into three groups and each group was given one of the three study drugs as per the details outlines below.

Group T₄ (n=30) received injection (inj) Thiopentone 4 mg/kg, Group T₃ (n=30) received thiopentone 3 mg/kg and midazolam 0.02 mg/kg, Group T₂ received thiopentone 2 mg/kg and midazolam 0.02 mg/kg intravenous as an induction agent. The observations are being tabulated in the table I as given below.

Table 1. The distribution of patients receiving different drugs with doses

Group	No. of patients	Drug used	
Group T ₄	30	3 ml Normal Saline	4 mg/kg thiopentone
Group T ₃	30	0.02 mg/kg midazolam	3 mg/kg thiopentone
Group T ₂	30	0.02 mg/kg midazolam	2mg/kg thiopentone

Various observations made before and after induction with study drugs is presented here along with the results that obtained. Mean age

Distribution of patients in years, mean weight distribution in kg, mean height distribution in cm in different groups are shown in table no. 2.

Table 2. Weight wise distribution of cases in each group

Weight In Kg	Group T ₄		group T ₃		Group T ₂	
	No.	%	No.	%	No.	%
41-45	4	13.3	6	20	6	20
46-50	6	20	7	23.3	3	10
51-55	2	6.6	6	20	8	26.67
56-60	2	6.6	7	23.3	4	13.3
61-65	9	30	0	0	3	10
66-70	2	6.6	1	3.3	2	6.6
71-75	3	10	2	6.6	4	13.3

DEMOGRAPHIC DATA

In Group T₄, mean age of the patients was 39.67 ± 11.75 years, mean weight was 55.4 ± 5.64 kg, mean height 150.73 ± 3.94 cm and male patients were 33.4% and female were 66.6 %.

In Group T₃, mean age of the patients was 34.46 ± 9.7 years, mean weight was 56.67 ± 6.81 kg, mean height 150.83 ± 4.8 cm and male patients were 40% and female were 60 %.

In Group T₂, mean age of the patient was 36.83 ± 9.65 years, mean weight was 57.16 ± 5.36 kg, height 152.36 ± 4.41 cm and male patients were 36.7% and female were 63.3 %. These demographic data are shown in the tables 2 and 3 and were not statistically significant in

terms of age, and weight indicating that these groups were similar.

Loss of verbal contact, occurred earlier in group T₃, (27.5 ± 3.1) seconds. The values for group T₄ were 29.1 ± 3.5 seconds and for group T₂ were 31.1 ± 3.9 seconds. These differences were significant.

Loss of eyelash reflex was earliest in group T₃, 32.3 ± 3.5 seconds. The values were 34.6 ± 4.1 and 42.1 ± 8 seconds in group T₄ and group T₂ respectively. Here also differences were significant.

Loss of response to a painful stimulus, patients in group T₃ achieved anaesthesia in the shortest time (46.3 ± 5.1 seconds). This was significantly less (p < 0.05) when compared with group T₄ (48.27 ± 5.8 seconds) and group T₂ (52.2 ± 6.2

seconds). Time taken by patients in group T₄ was also statistically significant as shown in the Table 3. was less than those in group T₂ and difference

Table 3. Age wise distribution of cases in each group

	Group T ₄		group T ₃		Group T ₂	
	Mean ± SD	P Value (T ₄ &T ₃)	Mean± SD	P Value (T ₃ &T ₂)	Mean± SD	P Value (T ₂ &T ₄)
Loss of verbal contact (in sec)	29.1 ± 3.5	< 0.05	27.5 ± 3.1	< 0.05	31.1 ± 3.9	< 0.05
Loss of eyelash reflex (in sec)	34.6 ± 4.1	< 0.01	32.3 ± 3.5	< 0.05	42.1 ± 4.24	< 0.05
Non responsive to painful stimulus (in sec)	48.27 ± 5.8	< 0.01	46.3 ± 5.1	< 0.05	52.2 ± 6.2	< 0.05

DISCUSSION

The good quality of induction is achieved when an Intravenous anaesthetic drug would provide hypnosis, amnesia, analgesia and muscle relaxation without undesirable cardiac and respiratory depression⁶. Because no single drug is ideal as an induction agent, many drugs are used often together, that offer some or all of the desired effects. Studies have revealed that the practice of combined anaesthetics drug use may be safer than the use of only one or two drugs.⁷.

Thiopentone is the most commonly used anaesthetic induction agent in our country. It has been the 'gold standard' for the induction of anaesthesia. Side effects are hypotension⁸⁻¹⁰ apnoea and adverse sequelae associated with the accidental extra vascular injection.¹¹⁻¹³.

In this study, we compared the two commonly used induction agents. Thiopentone and Sodium thiopentone-midazolam combination for the quality of induction in terms of time of loss of verbal contact, loss of eyelash reflex and loss of response to painful stimulus, hemodynamic stability. So we administered Sodium thiopentone-midazolam combination drug in a dose that is acceptable as low and safe (Sodium thiopentone 3 mg/kg and midazolam 0.02 mg/kg) in comparison to thiopentone dose 4 mg/kg body weight.

Another low dose combination of thiopentone and midazolam 2mg/kg and 0.02 mg/kg was also compared above two groups.

Our results showed that the duration of onset of sleep & the hemodynamic stability was comparatively better in Sodium thiopentone - midazolam combination (Sodium thiopentone 3 mg/kg and midazolam 0.02 mg/kg) group than thiopentone alone and low dose combination thiopentone and midazolam 2mg/kg and 0.02 mg/kg when used as the induction agent for general anaesthesia.

In our study, we had also compared the time of following induction of anaesthesia using either Sodium thiopentone-midazolam combinations or thiopentone. When compared between the three groups the onset of sleep assessed by the loss of verbal contact, loss of eyelash reflex and loss of response to painful stimulus was earlier in group T₃ (Sodium thiopentone -midazolam combination 3 mg/kg and 0.02 mg/kg respectively) than group T₄ (4 mg/ kg thiopentone alone) and T₂ (Sodium thiopentone -midazolam combination 2 mg/kg and 0.02 mg/kg respectively). This difference was considered to be statistically significant when compared within the groups.

This can be explained because both barbiturates and benzodiazepines are believed to act at the postsynaptic GABA receptors of the

CNS synapses by keeping open the chloride channel which in turn produces conduction blockade due to the chloride ion flow producing hyperpolarisation. According to Study and Barket¹⁴ (1981) as mentioned in the article by Short et al (1991),¹⁵ Benzodiazepines increase the frequency of chloride channel opening and barbiturates increase the duration of this open state. Thus one expects synergism from use of thiopentone and midazolam and that is what we have observed in our study. Not only the dosage of both drugs were less but also, the sedated state lasted longer than if either drug was used alone.

RESULTS

Duration of onset of induction was faster in Group T₃ (Sodium thiopentone -midazolam combination 3mg/kg-0.02mg/kg respectively) rather than Group T₄ (Thiopentone 4 mg/kg) and T₂ (Sodium thiopentone -Midazolam combination 2mg/kg-0.02mg/kg respectively) when used as the induction agent for general anaesthesia. Group T₃ had comparatively better hemodynamic stability during induction than Group T₄ and Group T₂.

CONCLUSION

It can be safely concluded that midazolam in a safe dose range reduces the dose of thiopentone for induction of anaesthesia. Thus many of the known depressant effects of thiopentone can be avoided. The haemodynamic stability during this co induction is significantly depressed when compared to thiopentone alone. Thus it can be concluded that thiopentone -midazolam co-induction with (3mg/ kg & 0.02 mg/ kg respectively) mg/kg midazolam should be encouraged for induction of general anaesthesia.

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REFERENCES

- [1]. Tom Lupton, and Oliver Pratt. Intravenous Drugs used for the Induction of Anaesthesia. Anaesthesia Tutorial of the Week (2007). Accessed 21st May, 2019, from https://www.wfsahq.org/components/com_virtual_library/media/58e0dbfafe77e5b30c1895379df8d444-Induction-Drugs-Used-in-Anaesthesia---Update-24-2-2008-.pdf.
- [2]. Khan, KS, Ivan H, and Donal J B. Pharmacology of anaesthetic agents I: intravenous anaesthetic agents. *Continuing Education in Anaesthesia Critical Care & Pain* 2014; 14(3): 100–105: <https://doi.org/10.1093/bjaceaccp/mkt039>.
- [3]. Garcia, P. S., Kolesky, S. E, Jenkins, A. General anesthetic actions on GABA(A) receptors. *Current neuropharmacology* 2010; 8(1): 2–9. doi: 10.2174/157015910790909502.
- [4]. Cohen MM, Duncan PG, Tate RB. Does anesthesia contribute to operative mortality? *JAMA* 1988; 260: 2859-2863.
- [5]. Koshy T.A. and Mahabala T. H. Midazolam-thiopentone mixture as an intravenous induction agent for general anaesthesia. Paper read during Annual Conference of I.S.A. held at Kathmandu, Dec. 1998.
- [6]. Ball C, Westhorpe R. The history of intravenous anaesthesia. The barbiturates. Part 2. *Anaesthesia Intensive care* 2001; 29:219.

- [7]. Cohen MM, Duncan PG, Tate RB. Does anesthesia contribute to operative mortality? *JAMA* 1988; 260: 2859-2863.
- [8]. Reves J, Gelman S. Cardiovascular affects of intravenous anaesthetics drugs. In Covino B, Fozzard H, Rehder K (eds): *Physiological Society*; 1985, p 179.
- [9]. Seljer J, Gerson I, Allen F. Comparison of the cardiovascular effect of bolus vs. incremental administration of the thiopentone. *Br J Anaesth* 1980; 52: 527-530.
- [10]. Eckstein JW, Hamilton WK, McCammond JM. The effect of thiopentone on the peripheral venous tone. *Anaesthesiology* 1961; 22: 525-528.
- [11]. MacPherson RD, McLeod LJ, Grove A1. Intra-arterial thiopentone is directly toxic to vascular endothelium. *Br J Anaesth* 1991; 67: 546-552.
- [12]. Mark LC. A lone case of gangrene following intra-arterial thiopentone 2.5%. *Anesthesiology* 1983; 59: 153.
- [13]. Vangerven M, Delru G, Brugman E, et al. A new therapeutic approach to accidental intra-arterial injection of thiopentone. *Br J Anaesth* 1989; 62: 98-100.
- [14]. Study R.E, and Barket, J. L in *Proceedings of the National Academy of Sciences, USA* 1981.
- [15]. Short T. G, Plummer J. L. et al. Hypnotic and anaesthetic action of thiopentone and midazolam alone and in combination. *Br J Anaesth* 1991; 66: 13-19.