

# Evaluation of Midazolam as an Intravenous Induction Agent for General Anaesthesia-Comparison with Thiopentone

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## ABSTRACT

**Introduction:** Midazolam, a water-soluble benzodiazepine, is non-irritant on intravenous injection and has a shorter duration of action than diazepam. In this research, we evaluated the induction time achieved with midazolam and compared with thiopentone. We also observed the hemodynamic effects following induction with midazolam and thiopentone. In the current study, we also studied undesirable or unwanted effects of the two drugs.

**Material and methods:** The present study was conducted at Civil Hospital, Aizawl Mizoram in the department of Anaesthesiology and Critical Care. The study was conducted between November 2018 to October 2019. A clinical study was carried out in hundred patients with a physical status of ASA I and ASA II patients, patients between 20-50 years of age and weight 45-70 kg were selected and were divided into two groups each group consisting of fifty patients. Group A – Midazolam (0.2mg/kg) and Group B – Thiopentone (5mg/kg). A routine preanaesthetic check-up was carried out before the operation. The procedure of anaesthesia to be given was explained to the patients and written informed consent was taken accordingly.

**Results:** The mean age (in years) of the midazolam group was  $35.54 \pm 8.5$  and it was  $34.06 \pm 10.2$  in the thiopentone group. We found a statistically significant difference of weight, spontaneous closure of eye, Loss of lid reflex between both the groups. Patient Good acceptance was good in 16 (66.67%) participants in midazolam and 8 (33.33%) participants in the thiopentone group.

**Conclusion:** We conclude that midazolam is a satisfactory substitute to thiopentone.

**Keywords:** Midazolam, Thiopentone, General Anaesthesia, Induction Agent

occur due to a structurally distinct group of drugs. Particular membrane proteins own peculiar binding sites that interact with injectable medications presently used for clinical anaesthesia.<sup>5</sup>

Midazolam, a water-soluble benzodiazepine, is non-irritant on intravenous injection and possesses a shorter duration of action than diazepam.<sup>6</sup> When compared with diazepam administered in an organic solvent water solubility reduces venous thrombosis and pain on injection. Midazolam is a hypnotic-sedative drug with anxiolytic and marked amnesic properties. Currently, in dentistry and endoscopic procedures, it has been used mainly by the intravenous route for sedation as an addition to local anaesthetic techniques.<sup>7</sup> Midazolam is a worthy premedial for regional or general anaesthesia. Induction of anaesthesia with midazolam alone is somewhat unpredictable; opiate pre-treatment makes induction more consistent.<sup>8</sup>

Since 1935 thiopentone sodium has been in use. It is a benchmark for comparing all other induction agents. Its use is associated with the lowest occurrence of complications and is possibly the most extensively used induction agent.<sup>9</sup> Thiopental, the thiobarbiturate analogue of the oxybarbiturate pentobarbital, was the most frequently used intravenous barbiturate in medicine and is prototypic of the group.<sup>4</sup> Thiopental is defined as ultrashort-acting; it induces anaesthesia of only short duration after a small dose is administered. If a patient is maintained under prolonged anaesthesia, however, by successive injections of thiopental, the period of subsequent continuing narcosis is also prolonged; it no longer behaves as an ultra-short-acting drug. This characteristic of thiopental has been ascribed to production and accumulation in the body of less active metabolic transformation products which have a long duration of action. This characteristic of drug action is one of its chief limitations and has restricted its un-supplemented

## INTRODUCTION

In the intensive care unit (ICU) therapy sedation is considered as a backbone due to its requirement by >85% of patients. Sedative drugs are used for assisting tolerance of endotracheal intubation, to manage agitation, mechanical ventilation, and invasive procedures.<sup>1,2</sup> Back in time during 1656, Daniel Johann Major and Percival Christopher Wren first experimented with IV administration using a goose quill and bladder to inject wine and ale into a dog's vein by which Intravenous (IV) anaesthesia can be traced back.<sup>3</sup> As intravenous anaesthetics, ultra-short-acting barbiturates were the first universally accepted drugs. The majority of knowledge about intravenous anaesthesia was generated through their use.<sup>4</sup> Anaesthesia through intravenous agents is a clinical state in which several behavioural endpoints

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use as a rule to surgical and obstetric procedures of relatively short duration.<sup>10</sup>

In this research, we evaluated the induction time achieved with midazolam and compared with thiopentone. We also observed the hemodynamic effects following induction with midazolam and thiopentone. In the current study, we also studied undesirable or unwanted effects of the two drugs.

## MATERIAL AND METHODS

The present study was conducted at Civil Hospital, Aizawl Mizoram in the department of Anaesthesiology and Critical Care after institutional ethical approval. The study was conducted between November 2018 to October 2019. A clinical study was carried out in hundred patients with a physical status of ASA I and ASA II patients, patients between 20-50 years of age and weight 45-70 kg were selected and were divided into two groups each group consisting of fifty patients. Group A – Midazolam (0.2mg/kg) and Group B – Thiopentone (5mg/kg).

Patients with neurological, renal, hepatic cardiovascular metabolic or endocrine dysfunctions, also pregnant and breast-feeding women were excluded from the study.

### Pre anaesthetic preparation

A routine preanaesthetic check-up was carried out before the operation. The procedure of anaesthesia to be given was explained to the patients and written informed consent was taken accordingly. Parameters including Chief complaint, history of present as well as past illness and treatment, previous experience to any anaesthetic agent, Personal history, history of habits, history of any drug allergy or drug therapy, menstrual history in females were recorded.

### Preparation of the patient

Patients were kept nil orally overnight. Oral diazepam, 0.2 mg/kg, was given the night before. Premedication with injection atropine 0.6mg promethazine injection 0.5 mg/kg and pethidine 1mg/kg intramuscularly were given one hour before the induction of anaesthesia.

### Induction and intraoperative period

Pre-oxygenation was done for three minutes. Pre induction recordings of blood pressure, pulse and respiration rate and were done, and induction was done with midazolam 0.2 mg/kg or thiopentone 5mg/kg over a period of 30 seconds. If the palpebral reflex was present for 60 seconds after the first dose, the second dose was given which is 50% of the first dose over a period of 15 seconds. Induction time which was taken as timing in second from induction to spontaneous closure of eyes and loss of lid reflex was observed. Recordings of blood pressure, pulse and respiratory rates at one-minute intervals for three minutes were done. Suxamethonium 1.5 mg/kg was used for tracheal intubation. Anaesthesia was maintained with oxygen, nitrous oxide, and halothane, pancuronium 0.1 mg/kg for muscle relaxation and controlled ventilation. Patients were extubated, suction was done and oxygen inhalational was given for 5 minutes or till the patients recover.

### Post-operative period

Nausea recordings were done by direct questioning of the

patient. Vomiting is recorded by a direct examination of the patients. The incidence of thrombophlebitis was recorded. The patient's acceptance with particulars reference to the induction phase was recorded. The information for each patient was elicited on a predesigned proforma. For analysis purpose information were transferred to a master chart, then fitted to the computer. With the help of SPSS, data were analysed by using a t-test, f-test and  $\chi^2$ -test wherever found suitable and necessary, and the interpretation was made accordingly.

## RESULTS

In the midazolam group, 16 (45.71%) participants were male and the remaining 19 (54.29%) participants were female. In the thiopentone group, 34 (52.31%) participants were male and the remaining 31 (47.69%) participants were female. The difference in the proportion of gender between the group was statistically not significant (P-value 0.529). The mean age (in years) of the midazolam group was  $35.54 \pm 8.5$  and it was  $34.06 \pm 10.2$  in the thiopentone group. The mean difference between the two groups was statistically not significant (P-value 0.465). The mean weight (in kg) of the midazolam group was  $53.80 \pm 4.9$  and it was  $53.88 \pm 2.6$  in the thiopentone group. The mean difference between the two groups was statistically significant (P-value  $<0.001$ ). The mean spontaneous closure of the eyes of the midazolam group was  $77.58 \pm 5.52$  and it was  $51.98 \pm 3.35$  in the thiopentone group. The mean difference between the two groups was statistically significant (P-value  $<0.001$ ). The mean loss of the lid reflex of the midazolam group was  $98.78 \pm 6.08$  and it was  $66.66 \pm 3.71$  in the thiopentone group. The mean difference between the two groups was statistically significant (P-value  $<0.001$ ) (table-1).

There was no statistically significant difference between two groups in systolic blood pressure pre-induction and 2 mints time periods. The mean systolic blood pressure 1<sup>st</sup> mints of the midazolam group was  $116.64 \pm 11.62$  and it was  $110.00 \pm 12.16$  in the thiopentone group. The mean difference between the two groups was statistically significant (P-value 0.009). The mean systolic blood pressure 3mints of the midazolam group was  $112.36 \pm 1.39$  and it was  $108.24 \pm 9.74$  in the thiopentone group. The mean difference between the two groups was statistically significant (P-value 0.014). There was no statistically significant difference between two groups in diastolic blood pressure pre-induction, 1 min, 2 mints and 3 mints follow up time periods. (Table 2)

There was no statistically significant difference between two groups in pulse rate pre-induction, 1 min, 2 mints, and 3 mints follow up time periods. There was no statistically significant difference between two groups in respiratory rate pre-induction, 1 min, 2 mints and 3 mints follow up time periods. (Table 3)

In the Midazolam group, 13 (72.22%) participants had nausea, 3 (16.67%) participants had vomiting and 2 (11.11%) participants had thrombophlebitis. In the thiopentone group, 21 (65.63%) participants had nausea, 5 (15.63%)

Parameter	Study group		P-value
	Midazolam (N=35)	Thiopentone (N=65)	
Gender (N(%))			
Male	16 (45.71%)	34 (52.31%)	0.529
Female	19 (54.29%)	31 (47.69%)	
Age (Mean $\pm$ SD)	35.54 $\pm$ 8.5	34.06 $\pm$ 10.2	0.465
Weight (Mean $\pm$ SD)	53.80 $\pm$ 4.9	53.88 $\pm$ 2.6	<0.001
Induction time (second)			
Spontaneous closure of eyes	77.58 $\pm$ 5.52	51.98 $\pm$ 3.35	<0.001
Loss of lid reflex	98.78 $\pm$ 6.08	66.66 $\pm$ 3.71	<0.001

**Table-1:** Comparison of background variables between the study group (N=100)

Time interval minute	Midazolam	Thiopentone	t- Value	P-Value
	Mean $\pm$ S. D	Mean $\pm$ S. D		
Systolic				
Pre- induction	122.40 $\pm$ 11.74	120 $\pm$ 10.59	1.46	0.300
1st Min	116.64 $\pm$ 11.62	110.00 $\pm$ 12.16	0.69	0.009
2 <sup>nd</sup> Min	109.96 $\pm$ 18.47	108.44 $\pm$ 9.94	0.51	0.593
3 <sup>rd</sup> Min	112.36 $\pm$ 1.39	108.24 $\pm$ 9.74	1.96	0.014
Diastolic				
Pre- induction	79.08 $\pm$ 8.18	77.60 $\pm$ 7.43	0.94	0.361
1st Min	76.04 $\pm$ 8.18	74.96 $\pm$ 6.91	1.32	0.486
2 <sup>nd</sup> Min	77.04 $\pm$ 8.51	74.72 $\pm$ 6.86	1.50	0.141
3 <sup>rd</sup> Min	77.04 $\pm$ 1.39	74.92 $\pm$ 7.11	1.36	0.085

**Table-2:** Comparison of blood pressure between the study group over four stages of time interval (minutes) (N=100)

Time interval minutes	Midazolam	Thiopentone	t-Value	P-Value
	Mean $\pm$ S. D	Mean $\pm$ S. D		
Pulse rate				
Pre – induction	88.86 $\pm$ 11.31	86.70 $\pm$ 11.39	0.95	0.367
1st minute	86.22 $\pm$ 9.92	82.78 $\pm$ 15.50	1.32	0.238
2 <sup>nd</sup> minute	86.46 $\pm$ 10.08	87.06 $\pm$ 10.56	0.29	0.784
3 <sup>rd</sup> minute	86.40 $\pm$ 10.11	87.98 $\pm$ 10.35	0.77	0.465
Respiratory rate				
Pre-induction	17.56 $\pm$ 1.34	17.14 $\pm$ 1.56	1.44	0.181
1 <sup>st</sup> minute	16.5 $\pm$ 1.22	16.24 $\pm$ 1.47	0.19	0.374
2 <sup>nd</sup> minute	16.68 $\pm$ 1.25	17.02 $\pm$ 1.51	1.25	0.257
3 <sup>rd</sup> minute	16.86 $\pm$ 1.30	18.97 $\pm$ 7.15	2.13	0.087

**Table-3:** Comparison of pulse rate and respiratory between study group over for stages of time interval (minutes) (N=100)

Complication	Study group		Chi square	P value
	Midazolam (N=18)	Thiopentone (N=32)		
Nausea	13 (72.22%)	21 (65.63%)	0.502	0.778
Vomiting	3 (16.67%)	5 (15.63%)		
Thrombophlebitis	2 (11.11%)	6 (18.75%)		

**Table-4:** Variation of complication between midazolam and thiopentone.

Patient Acceptances	Study group	
	Midazolam	Thiopentone
Good (N=24)	16 (66.67%)	8 (33.33%)
Satisfactory (N=70)	34 (48.57%)	36 (51.43%)
Bad (N=2)	0 (0%)	2 (100%)
Could Not Say (N=4)	0 (0%)	4 (100%)

**Table-5:** Variation of patient acceptances between midazolam and thiopentone

participants had vomiting and 6 (18.75%) participants had thrombophlebitis. The difference in the proportion of

complications between the study group was statistically not significant (P-value 0.778). (Table 4)

Out of 24 participants with good patient acceptance, 16 (66.67%) participants had midazolam and 8 (33.33%) participants had thiopentone. Out of 70 participants with Satisfactory patient acceptances, 34 (48.57%) participants had midazolam and 36 (51.43%) participants had thiopentone. Out of 2 participants with bad patient acceptances, all of them 2 (100%) participants had thiopentone only. Out of 4 participants with could not say patient acceptances, all of



them 4 (100%) participants had thiopentone. (Table 5)

## DISCUSSION

Any anaesthetic induction agent for day surgery should guarantee a smooth induction, immediate functional recovery with minimal postoperative sequelae and a rapid return to street fitness.<sup>11</sup> Thiopentone is still justifiably famous for inpatient procedures because of the smooth induction offered and in spite of the drug's known slow metabolism many anaesthetists continue to use this agent for day cases.<sup>12</sup>

Midazolam is a benzodiazepine and its clinical effects are sedation, motion control and anxiolytic. Its initial IV sedative dose is 0.05–0.1 mg/kg or 1 mg and then titrated to a max dose of 5 mg. As IV form, it has an onset of action near 2–3 minutes and the duration of sedation is 45–60 minutes.<sup>13</sup> In major surgery, midazolam is an alternative to thiopental for induction of anaesthesia in spite of its slow, variable induction time. Its advantages include excellent cardiovascular stability, transient and mild respiratory depression, low frequency of venous irritation, production of anterograde amnesia and short duration of action in comparison with other benzodiazepines.<sup>14</sup>

Induction involves the transition from an awake conscious state with intact productive reflexes to an unconscious state. Induction is accomplished when there is unresponsiveness to command and loss of eyelash reflexes.<sup>15</sup> In the present study, we evaluated midazolam as an agent for induction and compared its effects with thiopentone. After assessing gender, age and height in we found no significant difference among both the groups in these variables. We observed female predominance over the male in both groups. It was reported that induction time (second) for spontaneous closure of eyes and Loss of lid reflex was highly significant and less in the thiopentone group compared to the midazolam group. Similarly, Jensen, S et al<sup>16</sup>, in their study found that mean induction time was significantly shorter with thiopentone than with midazolam.

The current research showed a significant fall in systolic blood pressure between 1<sup>st</sup> to 3<sup>rd</sup> minute. We observed a significant fall of diastolic pressure from pre-induction to 2<sup>nd</sup> minute of post-induction in the thiopentone group otherwise no significant fall of diastolic pressure was observed. Lebowitz, PW et al<sup>17</sup> in their research concluded that Midazolam is, then, as acceptable for induction of anaesthesia as thiopental from a hemodynamic point of view in ASA. class I and II patients. Results of another study showed in the thiopentone group, intubation caused a mean rise in systolic arterial pressure from 141 to 193 mmHg ( $p < 0.0005$ ) and in the heart rate-systolic pressure product from 11101 to 21763 ( $p < 0.005$  in each case) and were relatively transient and returned to control values within 5 minutes.<sup>18</sup>

We found no significant difference in variation of pulse rate between both the groups. In a study the mean heart rate-systolic pressure products (Mean $\pm$ SD) for thiopentone were: control 7539 $\pm$ 584; at 2.5min 8359 $\pm$ 783; at 5min 8010 $\pm$ 718; at 10 min 7819 $\pm$ 974. For midazolam, these values were 7312 $\pm$ 542, 7 584 $\pm$ 645, 6327 $\pm$  573 and 6474 $\pm$  772 respectively.

None of the changes was statistically significant, either within each group or between groups.<sup>19</sup>

A study was done by Jensen, S et al<sup>16</sup>, found that the Mean ( $\pm$ SD) heart rate in the midazolam group was 70.9 $\pm$ 9.6 beat min<sup>-1</sup> before induction and this increased to 77.4 $\pm$  11.4 beatsmin<sup>-1</sup> 3min after the administration of the drug. Baseline means ( $\pm$ SD) heart rate in the thiopentone group was 69.0 $\pm$  11.0 beat min<sup>-1</sup> which increased 3min after injection to 75.7 $\pm$  11.6 beat min<sup>-1</sup>.

In the midazolam group, there was a highly significant fall in respiratory rate at 1<sup>st</sup> and 2<sup>nd</sup> minute and significant fall at 3<sup>rd</sup> minute. In the thiopentone group, a highly significant fall was observed at 1<sup>st</sup> minute. Patients showed a decrease in mean respiratory rate from 13.7 breaths/min to 12.8 breaths/min two minutes after injection of midazolam.<sup>20</sup> When midazolam is administered intravenously for induction of general anaesthesia, respiratory depression occurs through a marked decrease in the ventilatory response to carbon dioxide.<sup>21</sup>

Our study showed the lower post-operative incidence of nausea and vomiting was observed in midazolam compared to thiopentone with incidence thrombophlebitis was found more in thiopentone groups Study conducted by Abraham, J et al<sup>15</sup>, found postoperative nausea, vomiting and thrombophlebitis were significantly low with midazolam.

The present study revealed that the midazolam group had higher patient acceptance than the thiopentone group. Our results agreed with Abraham, J et al<sup>15</sup>, and Reves, JG et al<sup>22</sup>, as in their study patient acceptance was more for the midazolam group.

## CONCLUSION

The present study results showcased that as compared to thiopentone longer time was taken by midazolam to induce anaesthesia. We could observe a significant fall of systolic pressure and respiratory rate in both groups but in diastolic pressure, no significant fall was noted. Midazolam showed less incidence of nausea, vomiting and thrombophlebitis. Overall patient acceptance was higher in the midazolam group. We conclude that midazolam is a satisfactory substitute to thiopentone.

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