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Original Article

MIDAZOLAM AND THIOPENTONE AS CO-INDUCTION

Md. Habibur Rahman[1], Mahbub Hassan[2], Md. Monirul Islam[3]

ABSTRACT:

This study was undertaken to compare the induction characteristics of conventional thiopentone sodium, midazolam, and a combination of midazolam and thiopentone sodium as co-induction agent. Total one hundred and fifty patients of ASA grade I and II were divided into three groups in a double blind randomized study. Group-I received midazolam 0.25 mgkg^{-1} intravenously, group–II received thiopentone sodium 5 mgkg^{-1} intravenously and Group-III received midazolam 0.1 mg/kg^{-1} IV followed by thiopentone sodium 2.5 mg/kg^{-1} IV. Induction time was significantly prolonged with midazolam (group-II) compared to thiopentone sodium. The fall in systolic blood pressure (SBP) and diastolic blood pressure (DBP) was clinically insignificant in midazolam group. Induction with midazolam was not smooth and was associated with unwanted movement of limbs. Incidence of apnoea, pain, thrombophlebites were significantly less with midazolam. Co--induction with midazolam and thiopentone significantly reduced the induction time, unwanted movements of limbs, apnoea during induction and cardiovascular stability was also more in co-induction group than thiopenfone sodium group. Incidence and duration of drowsiness was also significantly lesser in co-induction group. These advantages signifies that combination of midazolan and thiopentone is better choice for induction of anaesthesia than the other conventional induction agent like individual midazolam or thiopentone.

INTRODUCTION:

Intra-venous anaesthetic agents are commonly used to induce anaesthesia, as induction is usually more rapid and smoother than inhalational agents. The induction agents available at present are not able to meet all properties of the ideal intravenous anaesthetic agents[1]. Although many drugs have been used and trailed as IV induction agent but only a few drugs have stood the test of time. Of them thiopentone sodium, midazolam, ketamine and propofol are important Thiopentone sodium is the drug, widely accepted for IV induction from long 1935. The advantages of thiopentone include rapid onset, reliability and smoothness of induction. However, recovery with thiopentone is delayed and this is a major disadvantage particularly in out patients anaesthesia, where the patients are expected to ambulate soon after surgery.

Ketamine has the advantage of good tissue tolerability and can be used either by intramuscular or intravenous routes. But it produces hypertonous, hypertension and emergence delirium and delayed recovery. Propofol is short acting with rapid onset and absence of excitatory effects. Beside these, there is a clear-headed recovery with this drug, which is very helpful for outpatient procedure. Pain on injection is a disadvantage. However, it is quite popular for induction and maintenance for short surgical procedures[2].

Midazolam hydrochloride an imidazole - benzodiazepine derivative synthesized in 1976 and was introduced into anaesthesia practice in 1981 as a water-soluble benzodiazepine with short duration of action[3]. This drug is now gaining popularity as an induction agent because of its smooth induction and less cardiovascular and other side effects. Induction time with midazolam has been reported to vary from 30 second to 2.55 minutes in various studies[4-5]. Pre-medication reduces induction time.

Midazolam acts synergistically with barbiturate, opioids, propofol. Induction dose of each of these agents can be lowered by 75% when it is combined

1. Associate Professor (C.C) Dept. of Anaesthesia, SBMC, Barisal
2. Professor (C.C) Dept. of Anaesthesia, Mymensingh Medical College.
3. Assistant Professor, BIRDEM, Medical College, Dhaka.

with other induction agents[6]. We conducted a study, where induction characteristics of thiopentone, midazolam and combination of midazolam with thiopentone as a co-induction were compared to find out better induction characteristics of anaesthesia.

MATERIALS AND METHODS:

The study was conducted at Sher-e-Bangla Medical College Hospital, Barisal after taking approval from local ethics committee. One hundred fifty patients scheduled for surgical procedures of about one hour duration were selected for study in prospective randomized manner. Patients of either sex, aged between 20-50 years and ASA grade I and II, were included after obtaining informed consent. Patients with severe cardiac, respiratory, hepatic and renal disease; pregnant patient and lactating mother were excluded. Patients with History of drug abuse, alcohol intake and psychotic disorder were also excluded from the study.

Patients were divided randomly into three groups. In Group-I, patients received thiopentone 5 mg kg^{-1}, Group-II, midazolam 0.25 mg kg^{-1} and Group-III, midazolam 0.125 mg kg^{-1} followed by thiopentone 2.5 mg kg^{-1} body weight.

An 18 gauge IV canula was inserted into the vein on the dorsum of the non-dominant hand. On arrival in the operation theater, base line blood pressure, heart rate, and oxygen saturation were recorded. An 20 gauge IV canula was also introduced into a suitable peripheral vein. The canula site was marked for later identification. Patients were continuously monitored for oxygen saturation, ECG and NIBP. Anaesthesia was induced with the alove drugs.

Time taken for loss of eyelash reflex was noted as the induction time. After induction, oxygen 6 L min^{-1} was given through a bain circuit. Tracheal intubation was facilitated with suxamethonium 1.5 $mgkg^{-1}$ and anaesthesia was maintained with a mixture of 60% N_20 and 0.5% halothane in oxygen. The blood pressure and heart rate were recorded at induction and at one minute, two minutes, 8 minutes of induction and at the end of operation. The patient were also observed at the post-operative ward for any complications like apnoea, desaturation, pain at the site of injection, urticaria, thrombophlebitis through the course of vein. Post-operative drowsiness was assessed on a four points scale:

O = Awake
I = Sedated but easily rousable on verbal commands.
II = Sedated but rousable on shaking or painful stimuli
III = Deeply sedated.

Reading were taken every 15 minutes for sedation in the post operative period and time taken to be widely awake (score-0) was noted. At the end of surgery, intavenous canula, which and was used for drug administration was removed. The site was checked for signs of any thrombophlebils after 24 hours. The results were statistically analysed by using students 't' test & Chi-square test.

RESULT

Demographic data is shown in Table-I. Age, sex, weight, ASA grade, induction time and duration of anaesthesia were comparable among all groups. The induction time of Group-I, Group-II & Group-III were 17.8+8.1 (Mean$\pm$SD) second (sec) 75.2$\pm$42.5 sec. and 35.5 ± 10.3 sec. respectively.

Statistical analysis revealed that induction time of midazolam (Group-II) was significantly longer than thiopentone (Group-I). But in Group-III (co-induction group), induction time was significantly shorter than midazolam (Group-II).

Table-I

Demographic data and induction time

	Group I	Group II	Group III
No. of patients (n)	50	50	50
Age (years)	36.5±12.6	38±13.1	34.3±11.5
Sex (M: F)	28:22	24:26	30:20
Weight (kg)	55.7±10.0	54.0±9.9	52±11.2
ASA grade (I : II)	40:10	38:12	42:8
Induction time (Sec)	17.8±8.1	75.2±42.5	35.5±10.3
Duration of Anaesthesia (min)	111.4±45	120.5±42.8	111.9±40.C

Mean ± SD, P <0.05 is considered significant

Table-II

Blood pressure and heart rate

Group	Parameter	Pre-induction	1 min—I min.	2 min.	8 min
I	SBP	126.9±13.8	112.5±14.5	111.3±15.6	118.5±5.9
	DBP	76.7±7.3	70.4±12.6	67.4±11.2	76.1±.2
	HR	80.8±10.7	10.6±13.1	111.5±12.3	92.3±1.6
II	SBP	115.2±12.2	110.5±12.9	109.9±9.4	114.1±2.5
	DBP	71.7±11.9	69.2±9.5	68.4±11.2	70.2±1.8
	HR	81.5±10.3	96.7±13.5	99.6±11.7	83.2±2.1
III	SBP	112.0±15.3	115.9±14:3	106±4.5	110±0.9
	DBP	78.4±11.8	70.4±12.9	70.5±1.4	77.2±1.1
	HR	86.5±12.9	94.2±11.4	97.5±2.9	87.9±2.4

Mean ± SD, P <0.05 is considered significant

SBP = System blood pressure, DBP = Diastolic blood pressure, HR = Heart rate

2 minute after induction of anaesthesia in Group-I, systolic blood pressure decreased to 111.3±15.6 mmHg from base line value of 126.9±13.8 mmHg. Reduction of BP was about 12%. In Group-II, SBP decreased from 115.2±12.2 mmHg to a minimum of 109.9±9.4 mmHg in the same period. Reduction of BP was about 4%. In Group III, SBP decreased from 112±15.3 to 106±14.5 (a reduction of 5%). In all these groups, fall in blood pressure were significant but fall is greater with thiopentone. Two min (2) after induction of anaesthesia, heart rate was seen to increase in all groups. But this increase was more prominent in thiopentone group.

Table-III

Adverse effects observed during induction

Group	Group-I	Group-II	Group-III
Redness	8(16%)	0	2(4%)
Pain at the site of inj.	7(14%)	01(2%)	2(4%)
Movement of limbs	2(4%)	22(44%)	5(10%)
Apnoea	19(38%)	6(12%)	8(16%)
Destruction	5(8%)	8(16%)	2(4%)
Dysrrhythmias	3(6%)	1(2%)	0
Cough	4(8%)	0	1(2%)

The incidence of redness was higher in Group-I (P<0.05). On the other hand none of the patient in Group-II had any incidence of redness. Pain at the site of injection was seen also higher in Group – I than other two groups. The high incidence of movement of limbs was seen midazolam group (Group – II) which was lowest in Group-I. The incidence of apnoea was significantly higher in thiopertone group (Group-I) compared to midazolam and co-induction groups. Drowsiness during postoperative period was higher (23) in Group-I, but it was lower in Group – III. Headache or heavy headedness was seen in 23 patients (46%) in Group-I; but it was vary low in midazolam & co-induction group. Postoperative nausea vomiting (PONV) was very high in thiopentone group than the other 2 groups. Thrombophlebites was seen in 3(6%) patients in Group I; and only 1(2%) patients in Group-III.

Table-IV

Postoperative characteristics

Characteristic	Group -I	Group -II	Group -IIII
Drowsiness	23(46%)	14(28%)	9(18%)
Headache	23(46%)	3(6%)	2(4%)
Nausea and vomiting (PONV)	15(30%)	6(12%)	5(10%)
Desaturation	2(4%)	0	0
Thrombophlebites	3(6%)	0	1(2%)

PONV = Postoperative nausea and vomiting

DISCUSSION:

It is well established that thiopentone sodium causes induction in one arm-brain circulating time[2]. The rapidity of induction is related to the dose, pre-medication, age of the patient and associated medical problems[6-7]. The induction time with midazolam was longer and there was wide variation of induction period among the patients. Berggren, et al (1981) evaluated midazolam in a dose of 0.36 $mgkg^{-1}$ and found that induction time was considerably longer (82.3±6.10 sec) in midazolam group than thiopentone group (45.9+1.7 sec)[8]. Al-Khudhairi found that mean induction time with midazolam (0.3mgkg-1) to be 30 sec. (ranges 12-45 sec) but the patients were premedicated with papavarine, hyoscine and droperidol one hour before surgery[4]. In our study, induction time was significantly shorter in co-induction group (Group-III) than the midazolam group, though it was longer than thiopentone group.

Crawford, et al found the mean induction time for midazolam to be 40 seconds where the patients were premeditated 30 minutes before induction with droperidol (5mg kg^{-1}) [9].

In our study, heart rate was increased by 30-40% in thiopentone induction, 15--20% in midazolan and co-induction groups. The fall in systolic and diastolic blood pressure at the end of 2 minutes was significant. Foster, et al[11] studied the haemadynamic affect of midazalam 0.15 mg kg^{-1} over 15 sec which produced statistically significant fall in systolic (57%) and diastolic (10%) blood pressure and increase in heart rate[10]. In Group-III, increase in heart rate and fall in blood pressure was minimum. The reduction in systemic vascular resistance may increase heart rate as a compensatory mechanism. This may be the main reason for thiopentone to produce a greater increase in heart rate[11].

Occurrence of redness and pain at the injection site in thiopentone group was significantly higher ($p<0.05$) than co-induction group (only 2 patients). Signs of thrombophlebites was seen in three patients of thiopentone induction but no patient developed thrombophlebitis in midazolam group. Only one patient in co-induction group developed signs of thrombophebites which was significantly less than thiopentone induction. Incidence of coughing was more in thiopentone group, which was absent with midazolam induction. Movement of limbs was more in midazolam group where as, limb movement was seen only in 2 patients (4%) in thiopantione group. The incidence was much less in co-induction group than midazolam induction. Higher incidence of movement of limbs was probably because of slower induction with midazolam or inadequate dose of midazolam used for induction[10].

A short period of apnoea developed in 19 patients (38%) in Group-I. The incidence was much less in midazolam and in co-induction group. The incidence of midazolam-induced apnoea in literature is more than we observed (18 to 78%)[12]. The incidence of post-operative nausea and vomiting (PONV) was more in thiopentone group, 15 (30%). It was seen in 6 patients (12%) in midazolam and 5 patients (10%) in co-induction group. Post-operative nausea and vomiting is a very common problem with an incidence of 3.6 to 85%[13]. In our study it was between 5% to 15%.

CONCLUSION

To conclude, midazolam when used in 0.25 $mgkg^{-1}$ body weight, takes significantly longer time for induction and the incidence of limb movement is higher. Induction with thiopurtonce is related with a significant change in cardiovascular parameters. Co-induction with midazolam and thiopentone in a reduced dose of each drug can shorter induction time and can reduce limb movements during induction. Recovery from anaesthesia was better with co-induction than thiopentone or midazolam. So, co-induction with midazolam-thiopentone can be a better choice than the indivudial indication agent like thiopentone or midazolam.

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