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Original Research Article

"Comparison the Induction Characteristics of Thiopentone, Midazolam and Propofol in Elderly Patients"

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Abstract: ***Background:*** Use of multiple anesthetic agents to induce anesthesia is not new and they are used to achieve different effects such as sedation, muscle relaxation and pain relief. Thiopentone is the most widely used intravenous induction agent in current anaesthetic practice. Propofol is a new rapidly acting intravenous anaesthetic. The rapid redistribution and metabolism of propofol, result in a short elimination half-life. Midazolam is an imidazobenzodiazepine with relatively rapid onset of action and high metabolic clearance compared to other benzodiazepine. ***Objectives*****:** T compare the induction characteristics of thiopentone, midazolam and propofol in elderly patients. ***Methods:*** A prospective randomized, double blind control study was conducted in the department of Anaesthesia at Shaheed Tajuddin Ahmad Medical College Hospital, Gazipur, Bangladesh from January to December-2020. Sixty three adult patients, aged between 55-75 years with ASA grade I & II Who were clinic trial in our department. The patients were divided into three groups of 21 each according to a randomization table. The overall performance of the drugs were assessed by recording the following parameters: 1. Pain on injection. 2. Induction time (The time from start of injection to the loss of eye lash reflex). 3. Coughing 4. Involuntary motor activity. 5. Apnoea (present/absent). 6. Haemodynamic changes (Heart rate and blood pressure at 2 min before injection, after induction and 1min, 3min and 5min after intubation). 7. Recovery time (From the end of reversal until the patient responded to vocal command (eye opening, tongue protrution). ***Results:*** The incidence of pain on injection was greater in propofol group (42.86%), which was statistically significant ($p<0.01$). The induction time was significantly longer ($p<0.001$) in the midazolam group. Incidence of excitatory effects was more common in propofol group ($p<0.05$). Incidence of apnoeic episodes were significantly greater in thiopentone and propofol group than midazolam group ($p<0.05$). Propofol caused significant decrease in systolic, diastolic and mean arterial pressure at 3 & 5 minutes after intubation ($p<0.001$).Neither Thiopentone, midazolam nor propofol caused significant change in heart rate. Recovery time in midazolam group was significantly longer ($p<0.001$). ***Conclusion:*** Thiopentone is the drug of choice for induction in elderly patients because of rapid induction, recovery and the least effect on arterial pressure. Propofol has no clear advantage over thiopentone and has the additional problem of a significant decrease in blood pressure. Midazolam, although safe, is clearly not the ideal drug for induction in elderly patients because of slow onset of action and delayed recovery.

Keywords: Induction Agent, Thiopentone, Midazolam, Propofol.

INTRODUCTION

Intravenous anaesthesia became possible with drugs available in 1930 and the concept rapidly became popular with patients and anaesthetists. Intravenous anaesthetic agents are commonly used to induce anaesthesia, for maintenance, may be administered as repeated bolus doses and also used for sedation in the intensive therapy unit (ITU) and treatment of status epilepticus. Propofol has been used in recent years as an effective alternative to the time-tested thiopentone for intravenous induction of anesthesia. Induction with propofol is smoother, almost equally rapid, has rapid awakening and orientation times, better intubating

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conditions and upper airway integrity compared to thiopentone sodium [1]. It has, however, a long half-life, which makes it less than ideal for use in ambulatory patients and can result in accumulation when used in repeated incremental doses or as a continuous infusion. A decrease of 26-28% of systolic blood pressure, 19% of diastolic blood pressure and 11% of mean arterial pressure (MAP) without changes in stroke volume and cardiac output are observed when anesthesia is induced with 2 mg/kg body weight of propofol [2, 3]. However, the major disadvantages of rapid induction with propofol are impaired cardiovascular and respiratory function which may put patients at greater risk from hypotension, bradycardia, and apnea. The rapid redistribution and metabolism of propofol, resulting in a short elimination half-life of approximately one hour suggest that the drug could be suitable for use in short procedure [2-4]. Optimal anaesthetic management of elderly patients depends on an understanding of the normal changes in physiology, anatomy and response to pharmacologic agents that accompany aging. Thiopentone is the most widely used intravenous anaesthetic agent in current anaesthetic practice. A number of other agents have become available as possible alternatives. Propofol (2, 6 diisopropyl phenol) is a new rapidly acting intravenous anaesthetic. A number of co-induction techniques have been investigated such as opioids [5], barbiturates like thiopentone sodium [6], and benzodiazepines like midazolam [7], Midazolam is an imidazobenzodiazepine. It is water soluble in acid formulation (pH less than 4) but becomes highly lipid soluble at physiological pH. It has a relatively rapid onset of action and high metabolic clearance compared to other benzodiazepines [8]. The pharmacokienetic of drugs are frequently defined in groups of healthy, normal, young male volunteers [9, 10]. The patients to whom the drugs are subsequently administered therapeutically however, are often elderly with perhaps multiple disease processes. As far as the elderly patients are concerned, agents that cause least physiological interference with rapid recovery have to be chosen. It is therefore, important to evaluate the effects of age on drug disposition.

MATERIALS AND METHODS

A prospective randomized, double blind control study was conducted in the department of Anaesthesia at Shaheed Tajuddin Ahmad Medical College Hospital, Gazipur, Bangladesh from January to December-2020. Sixty three adult patients, aged between 55-75 years with ASA grade I & II Who were clinic trial in our department. The patients were divided into three groups of thirty each according to a randomization table. In the control group, 21 patients received thiopentone and designated as thiopentone group. Midazolam and propofol were administered to two other groups of patients for induction of anaesthesia and designated as midazolam and propofol group respectively. All the patients were premedicated with diazepam at the dose of 0.2mg/kg body weight. After 3 minutes of preoxygenation anaesthesia was induced. The drugs were given through an 18G cannula in the dorsum of the hand. Thiopentone (intended dose 4mg/kg), midazolam (intended dose .2mg/kg) and propofol (intended dose 2mg/kg body weight) were injected sufficiently slowly to keep the haemodynamic stability by assessing clinically the rate and volume of the radial pulse until loss of eye lash reflexes. Tracheal tubes with an internal diameter of 8 mm in male 7 mm in female were inserted with the help of suxamethonium 1.5mg/kg using macintosh size 4 blade. The overall performances of the drugs were assessed by recording the following parameters: 1) Pain on injection. 2) Induction time (time from the start of injection to the loss of eye lash reflex). 3) Coughing 4) involuntary motor activity. 5) Apnoea (present/ absent).6 Haemodynamic changes (heart rate and blood pressure at 2 minutes before injection, after injection and 1 minute after intubation for 5 minutes). 7. Recovery time (from the end of reversal until the patient responded to vocal command eye opening, tongue protrution). Halothane was stopped 15 minutes before reversal and time from the end of reversal until the patient responded to vocal command was recorded. Results were expressed as mean ± SD. For statistical analysis student's 't' test, analysis of variance (ANOVA) and chi-square tests were applied where appropriate. Differences were considered statistically significant if $p<0.05$.

RESULTS

All the groups were comparable for age, sex, weight and duration of anaesthesia. Subject details are shown in (Table-1). The incidence of pain on injection is shown in (Table-2). The total incidence was greater in the group receiving propofol (42.86%), than in that receiving thiopentone (9.52%) and midazolam (4.76%). This difference was statistically significant. The time to induction (time to loss of eye lash reflex) was similar in the propofol and thiopentone group but significantly longer ($p<0.001$) in the midazolam group. This is shown in (Table-3). The number of patients showing spontaneous movement and excitatory effects is shown in (Table-4). The incidence of spontaneous movement was more common in the group receiving propofol ($p<0.05$). Three patients all of whom received propofol, showed spontaneous movement and one other complication (twitching, hypertonous, and hiccough). Five patients (23.3%), each in the thiopentone and propofol groups, required assisted ventilation because of apnoeic episodes that lasted more than 15 seconds, 2 patients in the midazolam group had apnoea that lasted longer than 15 seconds. This is shown in (Table-5). Changes in pulse rate from baseline (i.e before injection) are shown in (Table-6). Neither thiopentone, midazolam nor propofol caused a significant change in heart rate.

Table-1: Patient characteristics and duration of anaesthesia (N=63)

Group	Weight(kg)	Age(year)	Duration (hour)	Male	Female
Thiopentone(n=21)	53.3(±3.2)	67.5(±5.5)	1.5(±0.4)	16	5
Midazolam(n=21)	54.2(±4.6)	67.1(±4.9)	1.3(±0.6)	18	3
Propofol(n=21)	55.1(±4.3)	66.5(±5.5)	1.6(±0.3)	14	7

Table-2: Pain on injection (N=12)

Group	Mild	Moderate	Severe	Total	X^2 value
Thiopentone	2	0	0	2(9.52%)	
Midazolam	1	0	0	1(4.76%)	13.00
Propofol	5	2	2	9(42.86%)	
P<0.01					

Table-2: Induction time in seconds.

Group	Mean(±SD)	F value	P value
Thiopentone	31.8667(±1.2243)		
Midazolam	44.7000(±4.3164)	167.177	P<0.001
Propofol	31.1667(±1.7633)		

Table-4: Incidence of excitatory effects.

Group	Spontaneous Movements	Twitching	Hypertonous	Hiccough
Thiopentone	1	0	0	1
Midazolam	2	0	0	1
Propofol	6	1	1	2

Table-5: Incidence of apnoea after induction.

	Thiopentone	Midazolam	Propofol	X^2 value	P value
Apnoea>15 sec	5	2	5	6.882	P<0.05

Table-6: Comparison of heart rate at different reading points.

Group	2 minutes before injection-mean(±SD)	after induction-mean(±SD)	1minute after intubation-mean(±SD)	3minutes after intubation-mean(±SD)	5minutes after intubation-mean(±SD)
Thiopentone	75.0667	79.0667	85.0000	75.5333	74.9333
	(±2.1645)	(±2.1645)	(±4.4644)	(±2.5962)	(±2.4202)
Midazolam	74.9000	78.8333	86.6333	75.2667	75.1667
	(±2.0401)	(±1.9667)	(±6.8253)	(±2.0500)	(±1.6206)
Propofol	75.1000	79.1000	84.7000	76.1000	74.5333
	(±2.0569)	(±2.0569)	(±3.0530)	(±2.0569)	(±1.9070)
	F= .079	F=.149	F=.1.285	F=.1.074	F=.762
	N.S	N.S	N.S	N.S	N.S

N.S- not significant.

Table-7: Comparison of systolic blood pressure at different reading points.

Group	2minutes before injection-mean(±SD)	after induction-mean(±SD)	1minute after intubation-mean(±SD)	3minutes after intubation-mean(±SD)	5minutes after intubation-mean(±SD)
Thiopentone	142.1000	138.1000	150.3000	129.1000	130.1000
	(±17.0746)	(±17.0746)	(±17.7009)	(±17.0825)	(±16.0126)
Midazolam	137.4333	132.4333	148.1000	125.4333	127.4333
	(±14.5096)	(±13.1390)	(±17.0746)	(±14.5096)	(±14.1025)
Propofol	145.2000	135.2000	142.8333	115.2000	120.2000
	(±16.5413)	(±16.2415)	(±17.5501)	(±16.5413)	(±15.1360)
	F=1.773	F=.932	F=1.451	F=6.021	F=3.045
	N.S	N.S	N.S	P<0.01	P<0.05

N.S- not significant.

Table-8: Comparison of diastolic blood pressure at different reading points.

Group	2minutes before injection-mean(±SD)	after induction-mean(±SD)	1minute after intubation-mean(±SD)	3minutes after intubation-mean(±SD)	5minutes after intubation-mean(±SD)
Thiopentone	78.7667	74.5000	80.6000	75.4333	75.3215
	(±6.8917)	(±7.4776)	(±8.1351)	(±8.1988)	(±7.1897)
Midazolam	81.5000	72.5000	80.5316	72.5315	72.8132
	(±7.6010)	(±7.3215)	(±7.6218)	(±8.5369)	(±8.6758)
Propofol	80.7000	70.5734	77.1333	58.7210	60.7000
	(±7.3632)	(±7.3285)	(±6.9418)	(±7.3615)	(±7.3560)
	F=1.937	F=1.114	F=2.036	F=36.980	F=28.246
	N.S	N.S	N.S	P<0.001	P<0.001

N.S- not significant.

Table-9: Comparison of mean blood pressure at different reading points.

Group	2minutes before injection-	after induction-mean(±SD)	1minute after intubation-	3minutes after intubation-	5minutes after intubation-
	mean(±SD)		mean(±SD)	mean(±SD)	mean(±SD)
Thiopentone	99.8778	95.7000	103.7222	93.3222	93.6556
	(±8.0684)	(±8.5390)	(±7.5384)	(±9.3684)	(±9.3285)
Midazolam	100.1444	92.4778	103.0333	88.4778	89.3444
	(±7.5011)	(±7.5210)	(±7.9978)	(±7.4744)	(±7.9565)
Propofol	102.2000	92.2131	96.7444	77.5333	80.5314
	(±7.9344)	(±7.8352)	(±8.5383)	(±7.9339)	(±7.8356)
	F=.789	F=1.773	F=6.870	F=28.502	F=18.812
	N.S	N.S	P<0.01	P<0.001	P<0.001

N.S- not significant.

Table-10: Comparison of recovery time in seconds.

Group	Mean (±SD)	F value	P value
Thiopentone	23.0333(±3.2215)	177.284	P<0.001
Midazolam	44.3667(±7.8498)		
Propofol	21.8333(±3.0971)		

Details of arterial blood pressure values, systolic, diastolic and mean are shown in (Table-7, 8, 9). It can be seen that thiopentone caused some fall in systolic and little fall in diastolic blood pressure; mean arterial pressure consequently fall by an intermediate amount. Midazolam caused a greater decrease in systolic and diastolic blood pressure than thiopentone, but that was not significant. By contrast propofol caused a greater decrease in systolic blood pressure, which at 3 minutes after intubation had fallen by a mean of about 30 mm Hg, and a considerable fall in diastolic blood pressure, with a fall of about 20mm Hg. As a consequence, there was a considerable fall in mean arterial pressure. There was rise of blood pressure 1 minute after intubation in all the cases probably as a result of sympathetic stimulation due to intubation reflex. There was no significant difference in the recovery times between thiopentone and propofol groups. However, patients in the midazolam group took much longer to recover (p>0.001). This is shown in (Table 10).

DISCUSSION

Induction was smooth with propofol in comparison to thiopentone and midazolam. In the present study, high incidence of gag reflex coughing, tearing, movement of limbs was observed in thiopentone and midazolam groups compared to propofol. This finding was well correlated with observation of previous studies [11-13]. Mean seizure duration was significantly shorter with midazolam followed by propofol and thiopentone group. Though significant shortening of seizure duration was observed with propofol which was above 25 seconds, it does not affect modified ECT efficacy or therapeutic outcome. There has always been a need for an intravenous anaesthetic agent possessing a good induction and recovery characteristics, particularly in elderly patients. Elderly people differ both anatomically and physiologically from normal healthy adults. Moreover, they have got significant pharma- cokinetic and pharmacodynamic variability [14, 15]. Thiopentone is the most commonly used intravenous induction agent in

elderly people. There was no significant difference in the time to loss of eye lash reflex in the propofol and thiopentone groups. This supports previous findings that the induction characteristics are similar with two agents [16]. But Shah PJ *et al*. found that induction was rapid with propofol as compared to thiopentone which was statistically significant [6]. There was a sigficantly longer induction time with midazolam and this too in accordance with previous findings [9]. The incidence of spontaneous movements was greater in the patients who had received propofol than in those who received thiopentone and midazolam. The incidence of movement and excitatory effects after induction with thiopentone and midazolam was insignificant. Previous study by Shah PJ *et al*. found high incidence of gag reflex coughing, tearing, movement of limbs in thiopentone and midazolam groups compared to propofol [5]. But Rahman MH *et al*. showed that incidence of coughing was more in thiopentone group, which was absent with midazolam induction. Movement of limbs was more in midazolam group whereas limb movement was seen only in 2 patients (4%) in thiopentone group. Higher incidence of movement of limbs was probably because of slower induction with midazolam or inadequate dose of midazolam used for induction [5]. Suri Y found no excitatory effects with midazolam and thiopentone [13]. The incidence of pain on injection was significantly greater following propofol than after thiopentone and midazolam which was in consistent with previous findings [16]. Shah PJ *et al*. found that 20% of patients complained of pain on injection and 4.76% patients had thrombophlebitis with propofol compared 0% with thiopentone and midazolam [6]. Rahman MH *et al*. found that 14% of patients with thiopentone complained of pain on injection, where as 2% with midazolam [8]. Suri Y found that no patients with either thiopentone or midazolam experienced any venous intolerance [12]. In cases, where the drug was injected into a vein in the anticubital fossa, the incidence of pain was very low (4.76%) [15]. This feature may prove to be a drawback to its use in ambulatory patients as they are usually unpremedicated and often very anxious. The incidence of apnoea after induction with thiopentone and propofol was greater than that with midazolam. This was in consistent with previous findings [13-16]. This study has showed that thiopentone causes insignificant decrease in systolic, diastolic and mean blood pressure. There is no remarkable change in heart rate. Although midazolam caused a greater decrease in mean blood pressure compared to thiopentone that was not clinically significant. Cardiovascular stability was satisfactory during the observation period. Though some study had reported a significant decrease in mean arterial blood pressure 2 minutes after induction with midazolam, it was probably due to relatively higher induction dose [17]. There is however, a large variation in the recommended induction dose for midazolam (0.2– 0.4mg/kg). In this study propofol was found to have given a considerably greater fall in systolic, diastolic and mean blood pressure than did thiopentone. This persisted during the period under study in the propofol group. Earlier studies with propofol have reported similar results [16]. This persistently low blood pressure is an obvious disadvantage in the use of propofol in patients with a compromised cardiac function as in elderly people and a low initial blood pressure who need to be cardioverted e.g. ventricular tachycardia [16]. Singh *et al*. found that in patients with left ventricular dysfunction, there was a significant decrease from the baseline in the heart rate, mean arterial pressure after induction in all three groups of patients. The thiopentone group recorded the least decrease in heart rate (-7%), while the maximum decrease was seen in the midazolam group (-15%). The decrease in mean arterial pressure ranged from -27 to -32% and was similar across the three groups [6]. In hypertensive patients with thiopentone and midazolam co-induction, patients with unstable heart rate and diastolic blood pressure were more likely in thiopentone group and patients with stable heart rate and diastolic blood pressure were more likely in co-induction group [16]. The recovery times in this study suggested that there is no significant difference between propofol and thiopentone. Earlier study by Coolong KJ *et al*. had similar result where the surgical procedure continued longer than 2 hours [19]. This is in contrast to studies by Shah PJ *et al*. and Henriksson BA *et al*. which showed that propofol has significantly shorter recovery time than thiopentone [15]. Previous study had showed that flumazenil was used to reverse its effects 15 – 30 minutes after the induction of anaesthesia for cardio version, and there was however, an acceptably high incidence (50%) of resedation at the time of interview 4 hours later [20]. This could be explained by the very short procedures which they studied. In this study midazolam had a significantly longer recovery time than thiopentone and propofol. This is in consistent with previous findings [23].

CONCLUSION

Our findings suggest that thiopentone is the drug of choice for induction in elderly patients because of rapid induction, recovery and the least effect on arterial pressure. Propofol has no clear advantage over thiopentone and has the additional problem of a significant decrease in blood pressure. Midazolam, although safe, is clearly not the ideal drug for induction in elderly patients because of slow onset of action and delayed recovery.

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