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Midazolam and thiopentone co-induction: Looking for improvement in quality of Anaesthesia

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Abstract

Objective: To evaluate improvement in quality of anaesthesia induction using thiopentone and midazolam for co-induction of anaesthesia. An additional end point was taken as loss of response to a tetanic stimulation (50 Hz) delivered for 5 seconds after the loss of verbal contact and eyelash reflex.

Methods: Ninety ASA I and II patients, within the age range of 20-60 years were studied. Patients were randomly divided into three equal groups; A, B and group C

Results: Onset of induction and loss of response to a tetanic stimulation was achieved earlier in group B as compared to the other study groups ($p<0.05$).

Conclusion: Co-induction with midazolam 0.02 mg.kg-1 followed by thiopentone 3 mg.kg-1 was superior to other two groups. Induction of anaesthesia in this group was found to be smoother and faster, provided better hemodynamic stability, better airway maintenance and with lesser incidence of untoward effects (JPMA 53:542;2003).

Introduction

Co-induction is defined as the concurrent administration of two or more drugs that facilitate induction of anaesthesia.[1] It was criticized for a long time because of fear that combination therapy may also combine the side effects, thus increasing the risk to the patients.[2] Better understanding of the pharmacokinetics and pharmacodynamics as well as addition of many new drugs to the formulary has made it possible to accept the rational use of combination therapy.[3,4]

During the last decade co-induction of anaesthesia has been extensively studied with propofol in a number of combinations.[1-6] The most common disadvantages with propofol are its greater cost (Pak Rs. 330/-) as compared to Thiopentone (Pak Rs.52), high incidence of pain on injection[7] (50 - 100%) and relatively more hypotension as compared to thiopentone.[8]

Thiopentone is the most commonly used anaesthesia induction agent in Pakistan. Objective of our present study was to compare and evaluate co-induction of anaesthesia with a combination of thiopentone and midazolam and compare it to thiopentone induction alone. We also evaluated the quality of induction by observing an additional end point of hypnosis i.e., loss of response to a tetanic stimulus.

Methods

After approval from the Human Subjects Protection Committee of the university, informed consent was obtained from 90 ASA I and II patients who were then enrolled in the study in a blind, randomized and controlled manner. Blindness was ensured by preparation and administration of the drugs by an anaesthetist unconnected with the study. Subjects included both males and females between the age of 20 and 60 years, who were randomly, divided in three groups A, B and C. No premedication was given. Baseline systolic, diastolic, mean arterial pressure, heart rate and oxygen saturation with pulse oximetre was recorded using Datex cardiocap II monitor.

The study drugs were labeled as Drug 1and Drug 2. Drug 1was 3 mls of normal saline (placebo) in control group (A), while it was midazolam 0.02 $mg.kg^{-1}$ in group B and group C. Drug 2 was thiopentone 2.5% in a 25mls syringe. Thiopentone (Drug 2) was given in a dose of 4 $mg.kg^{-1}$ in group A patients, 3 $mg.kg^{-1}$ in group B patients and 2 $mg.kg^{-1}$ in group C patients, one minute after administration of Drug 1.

Haemodynamic parameters were recorded as baseline values, immediately following administration of Drug 1 and Drug 2 and every minute for five minutes. Patients were instructed to start counting loudly at the time of induction. Time of start of induction was noted. End point of hypnosis was assessed by noting the time of loss of verbal contact and loss of eyelash reflex. After the loss of eyelash reflex, a transcutaneous 50Hz tetanic stimulus was given for five seconds over the ulnar nerve at the wrist. The tetanic stimulus was taken as an equivalent of a painful stimulus[9,10] and patients were judged to be anaesthetized if they did not move in response of the tetanic stimulation.

Supplemental top up boluses of thiopentone (25 mg) were given to patients in whom anaesthesia was found to be inadequate, as judged by head or limb movements in response to tetanic stimulation. Total number of supplemental boluses of thiopentone were noted on the chart.

Any untoward effects like desaturation, bradycardia, tachycardia, hypotension, hypertension, dysrythmias, pain

on injection, hiccups and hypersensitivity reactions were also noted. Desaturation was defined as mild when oxygen saturation fell below 95% but remained above 90%, moderate between 86 % and 89 % and severe if it fell below 86%. Bradycardia was defined as the heart rate below 60 beats.min^{-1}, and tachycardia as heart rate above 100 beats min^{-1}. Hypertension was defined as blood pressure values (systolic, diastolic and mean), 20% above baseline and hypotension as 20% below the baseline values.

Statistical Analysis

Power analysis was used to determine the number of patients based on the assumption that for an α-value of 0.05 and a power (1-ß) of 0.8, 30 patients were required in each group. Variables were entered and analyzed on statistical package epi-info 6. The mean change in systolic, diastolic, mean arterial pressure, heart rate, and time to achieve anaesthesia were compared between the three groups using ANOVA. Categorical variables were compared using chi-square test; p-value of less than 0.05 was considered significant.

Results

Demographic data

Table 1 shows the demographic data. No significant difference was observed in age, weight and height between groups.

Table 1. Demographic data.

	No.	Age (years)	Weight (kgs)	Height (cms)
Group A	30	38.9±11	62.9±8.9	162.7±5.3
Group B	30	35.0±8.3	65.4±9.6	160.8±7.6
Group C	30	37.6±9.3	64.0±9.7	161.9±10.3

Hypnosis

The end point of hypnosis was assessed by loss of verbal contact, loss of eyelash reflex and loss of response to tetanic stimulation (50 Hz), as shown in table 2.

Loss of verbal contact, occurred earlier in group B (28.6 ± 6) seconds. The values for group A were 29.1 ± 5 seconds and for group C were 30.2 ± 6 seconds.

Loss of eyelash reflex was earliest in group B, 36.2 ± 8 seconds. The values were 39.4 ± 7 and 40.3 ± 8 seconds in group A and group C respectively.

Loss of response to tetanic stimulation. Patients in group B achieved anaesthesia in shortest time when this criteria was used as the end point of anaesthesia (40.6 ±8 seconds). This was significantly less ($p < 0.05$) when compared with group A (45.8 ± 7 seconds) and group C (50.4 ± 2 seconds). Although the time taken by patients in group A was less than those in group C but the difference was not statistically significant.

Table 2. Evaluation of hypnosis.

	Groups A	B	C
Loss of verbal contact (seconds)	29.1±5	28.6±6*	30.2±6
Loss of eyelash reflex (seconds)	39.4±7	36.2±8*	40.3±8
Loss of response to titanic Stimulation 50 Hz (seconds)	45.8±7	40.6±8*~	50.4±2

* =p<0.05, statistical difference between group A and B

~ = p<0.05, statistical difference between group B and C

Supplemental boluses requirement during induction

Top up supplemental boluses of thiopentone were given to patients who showed signs of inadequate anaesthesia e.g. head or limb movement on application of tetanic stimulation (50Hz). The group breakdown of number of supplemental bolus requirement is shown in table 3. Patients in group C needed significantly more top up boluses per patient as compared to the other groups. The difference was statistically significant when group A and B were compared with group C ($p<0.05$) for the total supplemental boluses given.

Table 3. Supplemental thiopental bolus requirement during induction.

Group	No.	No. of boluses 0	1	2	3
A	30	25	3	2	-
B	30	25	1	3	1
C	30	12	3	6	4

Cardiovascular data

Systolic blood pressure: the changes in systolic blood pressure compared to the baseline are shown in figure 1. The mean change in the systolic blood pressure was in positive direction. No significant difference in the magnitude of change was observed among the groups except between groups A and C, one minute after administration of drug 2 ($p < 0.05$). Systolic pressure in group B showed least variation from the baseline.

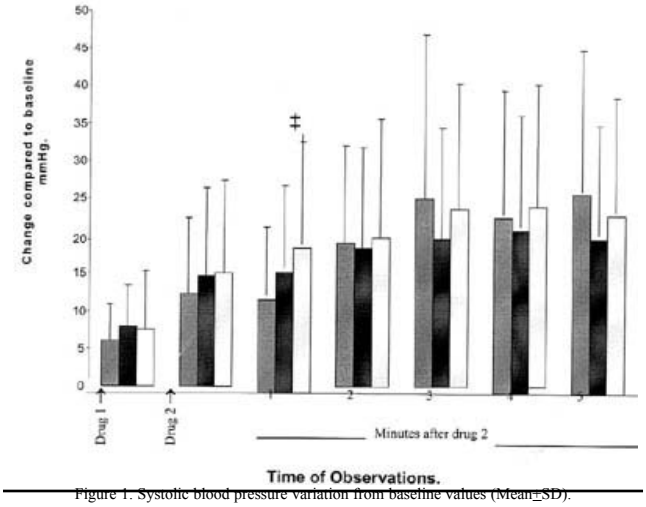


Figure 1. Systolic blood pressure variation from baseline values (Mean±SD).

Table 4. Change in oxygen saturation during induction.

Decline in oxygen saturation (%)		Groups A	B	C
Mild	90-95	14	13	16
Moderate	86-89	2	2	5
Severe	<86	1	1	0

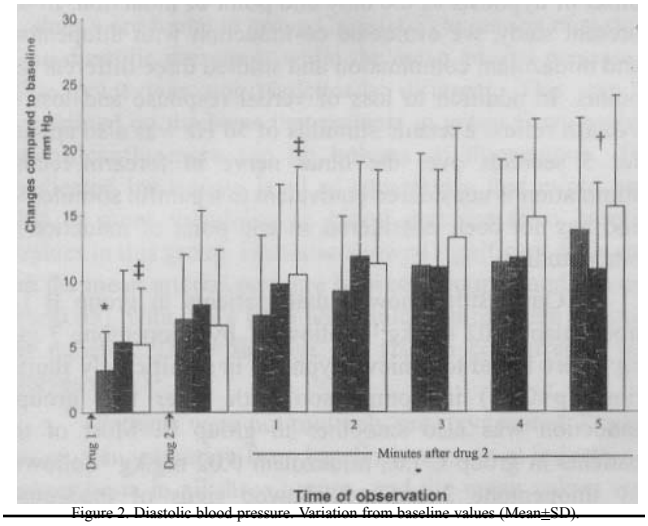


Figure 2. Diastolic blood pressure. Variation from baseline values (Mean±SD).

Diastolic blood pressure: These changes are shown in figure 2. Statistically significant difference in the magnitude of change was seen between groups A and B, and group A and C one minute after administration of drug 1. There was also significant difference ($p<0.05$) between groups A and C at one minute, and between group B and C at five minutes after administration of drug 2. Group B again showed the least variability.

Mean arterial pressure: The changes are shown in figure 3. Statistically significant difference was observed between group B and C at 5 minutes after giving drug 2 ($p<0.05$). The overall data showed a more stable mean arterial pressure in group B patients.

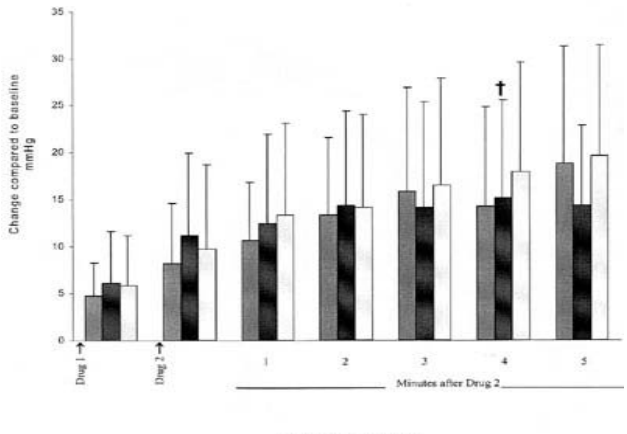


Figure 3. Mean arterial pressure. Variation from baseline values (Mean±SD).

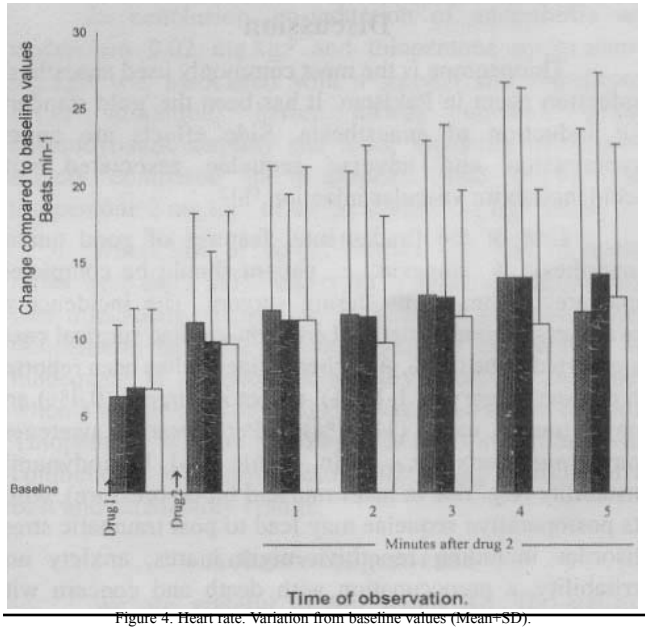


Figure 4. Heart rate. Variation from baseline values (Mean+SD).

Heart rate: The changes are shown in figure 4. Data showed no statistically significant difference between the groups but heart rate was clinically more stable in group B patients.

Complications

Desaturation: Seventeen patients in group A, 18 in group B and 21 patients in group C showed a decline in oxygen saturation from the baseline values. This data is presented in table 4. The values were not statistically

different between the three groups.

Bradycardia: Non of the patients in group B developed bradycardia as compared to four patients in group A and one in group B. The difference among the groups was not statistically significant.

Tachycardia: Five patients in group A, eight in group B and eight in group C developed tachycardia. This difference was not statistically significant.

Hypotension: Four patients in group A, three in group B and three in group C developed hypotension.

Hypertension: Two patients in group A, four in group B and seven in group C developed hypertension. The difference was not statistically significant.

Pain on injection: Three patients in group A, one in group B and non in group C complained of pain on injection.

Arrythmias: No patient developed arrhythmia in either group.

Hiccups: Only one patient in group B developed hiccups.

Hypersensitivity reactions: No patient in any group developed a hypersensitivity reaction.

Discussion

Thiopentone is the most commonly used anaesthesia induction agent in Pakistan. It has been the 'gold standard' for induction of anaesthesia. Side effects are apnea, hypotension and adverse sequelae associated with accidental extra vascular injection.[11,12]

One of the fundamental features of good quality anaesthesia is amnesia i.e., patient should be completely unaware of the events during surgery. The incidence of awareness in non-obstetrical and non-cardiac surgical cases is reported to be 0.2%. A higher incidence has been reported in cardiac surgery (1.1-1.5%), obstetric surgery (0.4%) and major trauma cases (11-41%).[13] Perioperative awareness may cause anxiety, pain, panic and hemodynamic instability (e.g. rise in heart rate and blood pressure), while its postoperative sequelae may lead to post traumatic stress disorder including repetitive night mares, anxiety and irritability, a preoccupation with death and concern with sanity.

Light anaesthesia is claimed to be the major factor responsible for awareness. In cardiac surgery and major trauma cases hemodynamic instability is the major concern at induction of anaesthesia. Fall in blood pressure associated with administration of thiopentone can aggravate this untoward effect. The dose of thiopentone is therefore reduced to avoid hypotension. Reduction of the dose of thiopentone may lead to awareness. Loss of verbal contact and loss of eyelash reflex has been taken as the endpoint of hypnosis by most of anaesthetists and the dose of thiopentone is titrated to achieve this end point. However observation of voluntary movements or movement response to noxious stimuli is the best clinical measure available for detecting wakefulness or impending wakefulness.[13] Premedication with amnesic drugs e.g., midazolam is recommended as one of the techniques to prevent awareness.

Midazolam, a water-soluble benzodiazepine is used as an intravenous induction agent in a dose of 0.125 to 0.2 $mg.kg^{-1}$. Side effects include apnea, mild burning sensation at the injection site and slight decrease in systolic blood pressure. Advantages include short duration of action and cardiovascular stability.[14,15] The sedative and hypnotic effects of barbiturates and benzodiazepines are mediated through separate receptors within the Gama amino-butyric acid (GABA) supra-molecular complex.[1] When used in combination, a synergistic interaction has been found between the two.[3,4,6,15] Barbiturates allosterically enhance benzodiazepine binding to the benzodiazepine receptors.[6] This interaction is mutual i.e., thiopentone potentiates the effect of midazolam and midazolam potentiates thiopentone.

Several authors have studied co-induction of anaesthesia with thiopentone and midazolam.[6,12,16] Some of the previous studies have shown that a low sub-hypnotic dose of midazolam (0.02 $mg.kg^{-1}$) reduces the induction dose of thiopentone by 50%.[1,4,6] These studies took the onset of hypnosis as the only end point of induction. In our present study, we evaluated co-induction with thiopentone and midazolam combination and studied three different end points. In addition to loss of verbal response and loss of eyelash reflex, a tetanic stimulus of 50 Hz was also applied for 5 seconds over the ulnar nerve in forearm.Tetanic stimulation is considered equivalent to a painful stimulus[9,11] and has not been considered an end point of induction in other studies.

Our results showed that, patients in group B i.e. midazolam 0.02 $mg.kg^{-1}$ followed by thiopentone 3 mg. kg^{-1} were found to achieve hypnosis in significantly shorter time ($p<0.05$) in comparison with other two groups. Induction was also smoother in group B. Most of the patients in group C i.e., midazolam 0.02 $mg.kg^{-1}$ followed by thiopentone 2 $mg.kg^{-1}$ showed signs of inadequate anaesthesia at the time of tetanic stimulation, although loss of verbal contact and loss of eyelash reflex in this group of patients was in accordance with the previous studies.[1,4,9]

The differences from other studies in the requirement of induction dose of thiopentone can be explained on the basis of observing loss of response to tetanic stimulus as an end point. The results can also be

interpreted as ' when hypnosis is taken as the end point of anaesthesia, midazolam 0.02 mg.kg^{-1} reduced the induction dose of thiopentone by 50%, but when tetanic stimulation was taken as the end point of anaesthetic induction, a 50% reduced dose of thiopentone was not sufficient to produce adequate anaesthesia. Co-induction with midazolam 0.02 mg.kg^{-1} and thiopentone in a dose of 3 mg.kg^{-1} on the other hand produced adequate anaesthesia when tetanic stimulation was taken as the end point. Co-induction with midazolam 0.02 mg.kg^{-1} also reduced the induction dose of thiopentone by 25%. This has been reported as 50% by other authors.[1,3,4]

Haemodynamic variation from baseline values was less in group B as compared to other groups but this difference was not statistically significant. There was a statistically significant difference ($p<0.05$) in both systolic and diastolic pressures when group B and group C were compared with group A at one minute after administration of drug 1. These findings are in accordance with those of Reves et al.[14] It is also explainable by the fact that in group A, drug 1 was placebo while in group B and C, drug 1 was midazolam 0.02 mg.kg^{-1}. The contributing factors may be relief from anxiety and consequently a slight decrease in blood pressure caused by midazolam. Mean arterial pressure at this point was not statistically different between the three groups.

When group A and C were compared one minute after giving thiopentone, greater variations from baseline values were found in group C ($p<0.05$) in respect of systolic and diastolic pressures, while the mean arterial pressure at this point was not statistically different. This can be explained on the basis that patients in group C were given significantly more top up boluses of thiopentone. This indicated inadequate level of anaesthesia that might have led to more variability in blood pressure from baseline values in this group. Data also showed significant difference in the mean arterial pressure between group B and group C ($p<0.05$), with more haemodynamic stability seen in group B patients. These findings are also in concurrence with Reves et al.[14]

Patients were not routinely pre-oxygenated. Decline in oxygen saturation from baseline was seen at induction of anaesthesia in all three groups, and the mean values were not different among the groups. The decline in oxygen saturation seen was less than reported by Throp et al.[17]

No significant difference was observed in the incidence of other untoward effects between the study groups. Clinically patients in group B developed lesser untoward effects when compared with group A and C. Although hypotension is commonly associated with thiopentone, bradycardia is unusual in patients with intact sympathetic reflexes.[18] The greater incidence of hypertension in group C can be explained due to inadequate anaesthetic levels.

Pain on injection is a known untoward effect with thiopentone due to its highly alkaline pH.[11] The incidence was low in group B where the dose of thiopentone was reduced by 25% and none in group C where the dose of thiopentone was reduced by 50%.

In our study, patients in group B were found to achieve hypnosis in significantly shorter time ($p<0.05$) in comparison with other two groups. Previous studies have assessed the degree of synergism between thiopentone and midazolam but in our study we have also additionally assessed the speed of induction by rating the time taken to achieve three anaesthesia end points.

Absence of response to a short painful stimulus indicated adequate depth of anaesthesia while greater hemodynamic stability at the same time in group B indicated better quality of anaesthesia in this group.

Conclusion

In conclusion, co-induction of anaesthesia with midazolam 0.02 mg.kg^{-1} and thiopentone midazolam 3 mg.kg^{-1} was associated with a smooth and significantly faster induction, better airway control, greater haemodynamic stability and lesser incidence of untoward effects compared to midazolam 0.02 mg.kg^{-1} and thiopentone 2 mg.kg^{-1} or thiopentone 4 mg.kg^{-1} alone.

When loss of verbal contact and loss of eyelash reflex were taken as the end point of induction, co-induction with midazolam 0.02 mg.kg^{-1} reduced the induction dose of thiopentone by 50% but this dose of thiopentone was inadequate to produce satisfactory level of anaesthesia when a tetanic stimulus (50 Hz) was taken as the end point. Thiopentone when reduced by 25% of its induction dose in combination with midazolam 0.02 mg.kg^{-1} produced the best and satisfactory results.

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