OPEN ACCESS

Haya: The Saudi Journal of Life Sciences
Abbreviated Key Title: Haya Saudi J Life Sci
ISSN 2415-623X (Print) | ISSN 2415-6221 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

"Co-Induction with a Small Dose of Ketamine is a Better Option Compared to Midazolam in Reducing Induction Dose of Propofol"

Md. Ashraful Anam[1*], Mohammad Jakir Hossen Mollick[2], Fakhruddin Ahmed[3], Md. Aminur Rahman[4], Sayed Nurul Huda[5], Mamata Manjari[6]

[1]Associate Professor, Dept. of Anesthesiology, Shaheed Tajuddin Ahmad Medical College, Gazipur, Bangladesh
[2]Assistant Professor, Dept. of Anesthesiology, Shaheed Tajuddin Ahmad Medical College, Gazipur, Bangladesh
[3]Assistant Professor, Dept. of Anesthesiology, Shaheed Tajuddin Ahmad Medical College, Gazipur, Bangladesh
[4]Associate Professor, Dept. of Anesthesiology, National Institute of Cancer Research & Hospital (NICRH), Mohakhali, Dhaka, Bangladesh
[5]Assistant Professor, Dept. of Anesthesiology, Chandpur Medical College, Chandpur, Bangladesh
[6]Assistant Professor (Gynae & Obs), Colonel Malek Medical College, Manikganj, Bangladesh

DOI: 10.36348/sjls.2022.v07i03.007 | **Received:** 11.02.2022 | **Accepted:** 15.03.2022 | **Published:** 30.03.2022

***Corresponding author:** Md. Ashraful Anam
Associate Professor, Dept. of Anesthesiology, Shaheed Tajuddin Ahmad Medical College, Gazipur, Bangladesh

Abstract

Background: Use of several anesthetic agents to induce anesthesia is not new and they are used to achieve different effects such as sedation, muscle relaxation and pain relief. Propofol has been accepted as an alternative to thiopentone for intravenous induction and is commonly used as an inducing agent and its action is more rapid. ***Objective:*** To compare co-induction with a small dose of ketamine is a better option compared to midazolam in reducing induction dose of propofol. ***Methods:*** This was a prospective, randomized, double-blind and interventional study conducted at Department of Anaesthesia, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh from January to December-2019. Fifty two adult patients undergoing elective surgery to be performed under general anesthesia were randomized to receive 0.3 mg/kg of Ketamine or 0.03 mg/ kg of Midazolam intravenously as co-induction agent. A minute after administration of co-induction agent, anesthesia was induced with Propofol 40 mg bolus then 10 mg every 10 seconds until the loss of verbal response. The hemodynamic response at 0, 1, 2, 5 minutes respectively and the induction dose of Propofol were noted. ***Results:*** A total of 52 patients (n=26 in each group) who met the inclusion criteria were included in this study. The patients where between age group of 20 years to 71 years and weight of 40 kg to 80 kg and had ASA physical status 1. As there were no significant differences in age, sex, weight and ASA physical status of patients, between the two groups, both of the groups were comparable. The mean arterial pressure heart rates were significantly lower at 1, 2 and 5 minutes in midazolam group. However, mean arterial pressure and heart were within the physiological range in both the groups. Propofol dose requirement for induction between the two groups was similar ($p>0.05$) but co-induction significantly decreased the induction dose of Propofol as compared to standard recommended dose for induction. ***Conclusion:*** Our study showed that hemodynamic variables were maintained within the physiological range with midazolam and ketamine co-induction. However, lesser degree of decrease in mean arterial pressure was seen with ketamine but the heart rate was higher. A similar reduction of induction dose of propofol was achieved with both the drugs.

Keywords: Combined anesthetic, Ketamine, Midazolam, Propofol.

Copyright © 2022 The Author(s): This is an open-access article distributed under the terms of the Creative Commons Attribution **4.0 International License (CC BY-NC 4.0)** which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use provided the original author and source are credited.

INTRODUCTION

Use of several anesthetic agents to induce anesthesia is not new and they are used to achieve different effects such as sedation, muscle relaxation and pain relief. Propofol has been accepted as an alternative to Thiopentone for intravenous induction and is commonly used as an inducing agent and its action is more rapid. Co-induction has been used to describe the practice of administering a small dose of a sedative or other anesthetic agent to reduce the dose of the induction agent required [1]. Midazolam has been

shown to reduce the dose of Propofol required to induce anesthesia by up to 50% without affecting the recover profile when used as" Co- Induction" [2]. Its onset is within 15 to 45 seconds and duration of action up to five to ten minutes [2]. It decreases arterial blood pressure due to a drop in systemic vascular resistance, cardiac contractility and preload. A typical anesthetic induction dose of propofol (2 mg/kg) results in an approximate 30% reduction in systolic blood pressure [3]. This effect is potentially injurious for cases with a compromised cardiovascular status. Propofol is an intravenous opiate narcotic which produces unconsciousness within 30 seconds after intravenous injection. The more rapid-fire return of knowledge with minimum residual central nervous affects is one of the most important advantages of Propofol. The induction cure of Propofol is 1.5 to 2.5 mg/ kg intravenous with blood position of 2 to 6 mg/ ml. It also depends on the associated specifics and the case's age [4]. It produces the drop in systemic blood pressure with bradycardia or no change in heart rate [5]. This effect is potentially deleterious for patients with a compromised cardiovascular status. Propofol is an intravenous sedative hypnotic which produces unconsciousness within 30 seconds after intravenous injection. The more rapid return of consciousness with minimal residual central nervous affects is one of the most important advantages of Propofol. The induction dose of Propofol is 1.5 to 2.5 mg/kg intravenous with blood level of 2 to 6 mg/ml. It also depends on the associated medications and the patient's age [4]. It produces the decrease in systemic blood pressure with bradycardia or no change in heart rate [5]. Ketamine is a phencyclidine derivative that produces dissociative anesthesia. Systemic and pulmonary arterial blood pressure, heart rate, cardiac output, cardiac work and myocardial oxygen requirement are increased after intravenous administration [6]. Midazolam is a benzodiazepine which increases the GABA mediated chloride ion conduction. It is used for premedication, anxiolysis, sedation, induction and co-induction of anaesthesia [5]. Midazolam is a benzodiazepine with potent amnesic effect than sedation. Induction dose causes greater decrease in systemic blood pressure and increase in heart rate. Most significant side effect of Midazolam is depression o ventilation caused by decrease in the hypoxic drive [7]. Since Midazolam is commonly used as a co-induction agent with Propofol, thinking of an alternative choice, the prospective study was designed to compare Ketamine with Midazolam as a co-induction agent with Propofol.

MATERIALS AND METHODS

This was a prospective, randomized, double-blind and interventional study conducted at Department of Anaesthesia, Department of Anaesthesia, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, Bangladesh from January to December-2019. Fifty Two patients of age 20 to 71 years of ASA I and ASA II, undergoing elective surgery to be performed under general Anesthesia were randomly selected and divided into two groups. Patients in group K received 0.3 mg/kg of Ketamine and group M received 0.03 mg/kg of Midazolam intravenously before induction agent propofol was administered.

Anesthetic Technique

Patients enrolled into the study were randomly divided into one of the two groups by lottery method-Group M scheduled to receive Midazolam 0.03mg/kg body weight before induction with propofol Group K scheduled to receive Ketamine 0.3 mg/kg body weight before induction with propofol. On the day of surgery, in the operation theatre, peripheral venous access was secured and monitors for vital parameters (heart rate, Electrocardiogram, Blood pressure, pulse oximeter) were attached. The co-induction agent was prepared in a 5ml syringe by another Anesthesiologist or Anesthetic assistant who did not take part in the study. Pethidine 0.5mg/kg and the co-induction agent were given intravenously. The patient in group M received 0.03mg/ kg of Midazolam and the patient in group K received 0.3 mg/kg of Ketamine. One min after the co-induction agent patients were induced with Propofol 40mg bolus then 10 mg every 10seconds until the loss of eye lash reflex and verbal response. Face mask was applied tightly at this point and with any response to the placement of mask additional bolus of Propofol 10mg was given. At the end of the surgery patients were reversed with Neostigmine 0.05mg/kg and Atropine 0.025mg/kg. Patients were shifted to post anesthetic care unit after extubation of trachea. Demographic variables were noted. Heart rate (HR) and Mean Arterial Pressure (MAP) were recorded pre-operatively, 1, 2 and 5 minutes.

STATISTICAL ANALYSIS

Sample size was calculated considering type I error of 0.05 and power 0.80, assuming a percentage change in mean of 20% and percentage coefficient of variation of 30% in dose of propofol between two groups. Statistical test: student's T-test and X^2 tests were applied for the comparison and P value <0.05 was considered as significant.

RESULTS

Out of 52 patients (n=26 in each group) who met the inclusion criteria were included in this study. The patients where between age group of 20 years to 71 years and weight of 40 kg to 80 kg and had ASA physical status 1. As there were no significant differences in age, sex, weight and ASA physical status of patients, between the two groups, both of the groups were comparable (Table-1).

© 2022 |Published by Scholars Middle East Publishers, Dubai, United Arab Emirates

Table-1: Demographic distribution (N=52)

Group	Midzolam	Ketamine	P value
Age in years (mean±SD)	37.48 ± 9.43	38.48 ± 12.05	0.731
Sex (M/F)	4/22	5/21	1.0
ASA I	26	26	1.0
Weight in kg	55.92 ± 12.27	55.76 ± 10.001	0.96

There was significant decrease in heart rate in the Midazolam group after induction of anesthesia at 1, 2, and 5 minutes. But, it initially increased from baseline in the ketamine group at one and two minutes. Heart rate in the ketamine group remained significantly higher at all times of observation (Table 2).

Table-2: Heart rate in beats/ minutes (N=52)

Group	Midazolam	Ketamine	P value
Baseline (Mean ± SD)	87.48 ±16.008	87.92 ±19.4	0.93
1 minute after co-induction (Mean ± SD)	76.84 ±15.98	91.68 ±13.93	0.001
2 minute after co-induction (Mean ±SD)	74.80 ±13.48	89.48 ±13.98	0.000
5 minute after co-induction (Mean ±SD)	75.56 ±12.53	84.88 ±15.73	0.025

The baseline Mean arterial blood pressure (MAP) was measured and also recorded at 1, 2 and 5 minutes after induction. There was a significant decrease in MAP at 1, 2 and 5 minutes after induction of anesthesia in the Midazolam group (Table 3).

Table-3: Mean arterial pressure in mm of Hg (N=52)

Groups	Midazolam	Ketamine	P value
Base line MAP	94.68 ± 13.06	93.04 ± 12.12	0.648
MAP at 1 minute	82.40 ± 12.92	89.28 ± 8.93	0.034
MAP at 2 minute	75.40 ± 10.41	83.32 ± 9.23	0.007
MAP at 5 minute	78.12 ± 10.146	85.04 ± 9.145	0.015

For induction of Anesthesia 40 mg of Propofol was given as a bolus dose in both of the groups irrespective of weight and age of the patient followed by additional dose of 10 mg Propofol every 10 seconds until there was loss of verbal response. The induction dose of Propofol required in the two groups did not differ significantly and is shown in the following (Table 4).

Table-4: Total induction dose of Propofol (in mg) (N=52).

Groups	Midazolam	Ketamine	P value
Total induction dose of Propofol (Mean ± SD)	55.60 ± 17.81	54.80 ± 15.84	0.867

DISCUSSION

In our study 52 patients undergoing routine surgical procedures under general anesthesia were selected and randomly divided into two groups as group M- Midazolam and K-Ketamine group of 26 patients each. The two groups were comparable in terms of age, and base line hemodynamics. All patients received Pethidine 0.5 mg/kg as an analgesic. Then patients in group M received 0.03 mg/kg of Midazolam and patients in group K received 0.3 mg/kg of Ketamine as a co-induction agent. One minute after co-induction the patients were given 40 mg of Propofol irrespective of weight. The technique of co-induction using two or more agents to induce anaesthesia has been studied and synergism has been reported between a number of induction agents and Midazolam [7]. The potential benefits of synergism in clinical practice would mean that anaesthesia could be induced with a smaller combined total of anaesthetic agents with fewer side effects. The hemodynamics was observed at 1, 2, 5 minutes respectively and this was the end point of the study before maintenance of anesthesia and endotracheal intubation was performed. We observed the hemodynamics at these intervals because we used noninvasive blood pressure monitoring. A more frequent noninvasive blood pressure monitoring interval may lead to less reliable reading of blood pressure. The result of our study showed that there was significantly lower in Heart rate in Midazolam group as compared to Ketamine group at all times of observations that is 1, 2, and 5 minutes following co-induction (p value < 0.05). The highest fall in Heart rate was noticed at 2 minutes in Midazolam group as compared with Ketamine. In a similar study done by Sirvastava *et al*. [8] in 2006 among 68 ASA I and II patients undergoing elective surgery under general anesthesia they found that there was a fall in Heart rate and MAP in all groups but there

© 2022 |Published by Scholars Middle East Publishers, Dubai, United Arab Emirates

was a significant fall in Heart rate and mean arterial blood pressure in saline group compared to Ketamine group whereas there was no significant difference in Heart rate and mean arterial blood pressure between Midazolam and saline group. All the patients in their group received Fentanyl but in our study we used Pethidine. The induction dose was given 1 minute after co-induction in our study but they induced 2 minutes following co-induction. Their study did not compare between Midazolam and Ketamine group as compared to our study. Our study showed that there was a significant decrease in blood pressure and heart rate in the midazolam group but it remained within the physiological range. Ong and Osborne *et al*. [9] in studied the effect of Ketamine co-induction to Propofol on Propofol induction doseand hemodynamics. They found a significant reduction in Heart rate and mean arterial blood pressure in saline group compared to Ketamine group at the time of induction (that is 2 minute after co-induction). They did not find any significant difference between the two groups in terms of Heart rate and mean arterial blood pressure at other times of observation. In our study we found significant difference in Heart rate and mean arterial blood pressure at all time of observation between the two groups with higher heart rate and MAP with the use of Ketamine. Their study did not find any significant difference in Heart rate and mean arterial blood pressure following induction in Midazolam group compared to saline group. They compared Midazolam with saline group but our study compared Ketamine with Midazolam group. In our study we found Midazolam significantly decreased Heart rate and mean arterial blood pressure compared to Ketamine. Propofol is a choice for intravenous induction of anesthesia because of its faster onset and quick recovery. The recommended induction dose of Propofol is 1.0 to 2.5 mg/ kg [10]. The average weight of the patients in our study was 55.92 kg in Midazolam group and 55.76 kg in Ketamine group. If we use propofol in a recommended dose of 2 mg/ kg, they would require 111.84 mg of Propofol in Midazolam group and 111.52 mg in Ketamine group. However in our study we found that in Midazolam group, the patients required 55.60±17.81 mg of Propofol for induction and in Ketamine group, they required 54.80 ± 15.84 mg of Propofol. So our study shows that both the co-induction agents were effective in reducing the dose of Propofol. Propofol is known to cause significant reduction in MAP and heart rate. As co-induction was found to decrease the dose requirement of Propofol for induction, the hemodynamic stability seen can also be due to the lower dose of Propofol used for induction of anesthesia.

CONCLUSION

The present study showed pre-dosing with Propofol is less effective than Midazolam in reducing the dose of Propofol to induce anaesthesia. Propofol is a generally used intravenous induction agent because of its fast onset and quick recovery but a well- known side effect is unstable hemodynamics. Co-induction with ketamine was associated with lower change in mean arterial pressure and heart rate. Coinduction significantly dropped the induction cure of Propofol as compared to standard recommended cure but, the cure reduction of Propofol for induction of anesthesia wasn't significant between the groups.

REFERENCES

1. Amrein, R., Hetzel, W., & Allen, S. R. (1995). Co-induction of anaesthesia: the rationale. *European journal of anaesthesiology. Supplement*, *12*, 5-11.
2. Short, T. G., & Chui, P. T. (1991). Propofol and midazolam act synergistically in combination. *British journal of anaesthesia*, *67*(5), 539-545.
3. Short, T. G., Plummer, J. L., & Chui, P. T. (1992). Hypnotic and anaesthetic interactions between midazolam, propofol and alfentanil. *British Journal of Anaesthesia*, *69*(2), 162-167.
4. BrysonHM, F. (1995). FauldsD. Propofol: an updateofitsuseinanaesthesiaandconscioussedation [J]. *Drugs*, *50*(3), 513-559.
5. Cressey, D. M., Claydon, P., Bhaskaran, N. C., & Reilly, C. S. (2001). Effect of midazolam pretreatment on induction dose requirements of propofol in combination with fentanyl in younger and older adults. *Anaesthesia*, *56*(2), 108-113.
6. Tweed, W. A., Minuck, M., & Mymin, D. (1972). Circulatory responses to ketamine anesthesia. *The Journal of the American Society of Anesthesiologists*, *37*(6), 613-619.
7. Collins, L. M., Cooney, C. M., & Fitzpatrick, G. (1997). Propofol induction characteristics after fentanyl or midazolam and fentanyl. *Br J Anaesth*, *79*, 676-7P.
8. Srivastava, U., Sharma, N., Kumar, A., & Saxena, S. (2006). Small dose propofol or ketamine as an alternative to midazolam co-induction to propofol. *Indian J Anaesth*, *50*(2), 112-114.
9. Ong, E. L., & Osborne, G. A. (2001). Ketamine for co-induction of anaesthesia in oral surgery. *Ambulatory surgery*, *9*(3), 131-135.
10. Asida, S.M. (2004). Midazolam co-induction in the elderly. *El-Minia Med Bull*, 15; 300-7.
11. Hui, T. W., Short, T. G., Hong, W., Suen, T., Gin, T., & Plummer, J. (1995). Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. *The Journal of the American Society of Anesthesiologists*, *82*(3), 641-648.

© 2022 |Published by Scholars Middle East Publishers, Dubai, United Arab Emirates