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"The Effectiveness and Evaluation the Use of Midazolam, Ketamine and Propofol as Co-Induction Agents To Propofol For General Anesthesia"

I.R.M. Sazzad Haider[1], Tayeba Haque[2], Mizanur Rahman[3]
[1]*Junior Consultant (Anesthesia), Sheikh Russel National Gastroliver institute and hospital, Mohakhali, Dhaka, Bangladesh*
[2]*Junior Consultant (Anesthesia), Shahid Ahsanullah Master General Hospital, Tongi, Gazipur, Bangladesh*
[3]*Junior Consultant (Anesthesia), Sheikh Fazilatunnessa Mujib Eye Hospital & Training Institute, Gopalgonj, Bangladesh*
Corresponding Author: I.R.M. Sazzad Haider,
Junior Consultant (Anesthesia), Sheikh Russel National Gastroliver institute and hospital, Mohakhali, Dhaka, Bangladesh

Abstract
Introduction: *Propofol is an IV anaesthetic agent with hypnotic, sedative, and amenestic properties, which cause loss of consciousness reliably and rapidly. It is considered as first choice drug for day care surgeries due to short elimination half-life, high plasma clearance, and intrinsic anti emetic features*
Objective: *To The effectiveness and evaluation the use of midazolam, ketamine and propofol as co-induction agents to propofol for general anesthesia.*
Methods*: This randomized, controlled, prospective, double-blind, clinical trial study was carried out at the Dept. of Anesthesia, Sheikh Russel National Gastroliver institute and hospital, Mohakhali, Dhaka, Bangladesh from January to June 2021. Sixty patients with American Society of Anaesthesiologist (ASA) physical status I and II, aged 18-65 years, of either sex, undergoing day-care surgeries requiring general anaesthesia were included in this study. The patients were randomly allocated into two equal groups. Group A received ketamine-propofol and Group B received midazolam-propofol for induction of anaesthesia. All the patients received pethidine 0.8 mg/kg. Two minutes after the administration of co-induction agent, each patient received 20 mg of lignocaine and injection propofol was given 10 mg every five seconds until patient stopped counting and does not respond to a reminder to continue counting. The level of sedation and alertness was targeted to an observer's assessment of alertness/ sedation score of 2.*
Results*: Mean induction dose of propofol in the two groups was compared by student's T test. The mean induction dose was 53.67 (30-120) mg in Group A and 52.33 (30-110) mg in Group B. The difference between the mean inductions doses of propofol in the two groups were statistically insignificant (P-value of 0.78). Mann Whitney test was also used to compare the mean induction doses of propofol between the two groups. The difference in mean induction doses of propofol was statistically insignificant (P-value of 0.57).*
Conclusion*: In conclusion,there is no difference in the mean induction dose of propofol with ketamine-propofol and midazolam- propofol co-induction. The possible reasons for this insignificant difference might be the gender differences between the two groups. More studies are required in a larger population of patients, and in same gender and comparison between genders to rule out if gender has some effect on the dose requirements of the patients.*

Keywords: *Co-induction, Ketamine, Propofol, Midazolam, Outcome.*

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I. Introduction

Propofol is an IV anaesthetic agent with hypnotic, sedative, and amenestic properties, which cause loss of consciousness reliably and rapidly. It is considered as first choice drug for day care surgeries due to short elimination half-life, high plasma clearance, and intrinsic anti emetic features [1]. The term 'co-induction' has been used to describe the practice of administering a small dose of a sedative or other anaesthetic agent to reduce the dose of induction agent [2, 3]. Its onset is within 15 to 45 seconds and duration of action up to five to ten minutes [4]. 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 [5]. This effect is potentially deleterious for patients with a compromised cardiovascular status. Co-induction refers to the administration of a small dose of sedative or other anaesthetic agent prior to the induction of anaesthesia to reduce the dose of induction agent, and to achieve more specific responses while minimizing side effects [5]. This large dose needed for induction may be associated with haemodynamic and respiratory effects like hypotension, [6] bradycardia, apnoea or hypoventilation [7]. Midazolam when used in sub-anaesthetic doses reduces the dose of Propofol required for induction via a synergistic action [8]. This practice of administering a small dose of sedative or other anaesthetic agent viz. midazolam, ketamine, propofol (auto co-induction), fentanyl, alfentanil to reduce the total dose of the induction agent is known as co-induction [9]. In contrast to other anaesthesic agents, ketamine increases arterial blood pressure, heart rate and cardiac output. It should be avoided in patients with coronary artery disease, uncontrolled hypertension, congestive heart failure, increased intracranial pressure (ICP) and arterial aneurysms. The incidence of its psychomimetic effects can be reduced by co administration of benzodiazepine, barbiturate, or propofol[10]. Thus, the need for anaesthetic agent arises which provides stable haemodynamics, good analgesia, rapid recovery, early ambulation and minimal complications [11]. Propofol is considered as an anaesthetic agent of choice.

II. Materials and Methods

This randomized, controlled, prospective, double-blind, clinical trial study was carried out at the Dept. of Anesthesia, Sheikh Russel National Gastroliver institute and hospital, Mohakhali, Dhaka, Bangladesh from January to June 2021. The patients included in this study were those belonging to American Society of Anaesthesiologist (ASA) physical status I and II, aged 18 to 65 years of either sex, undergoing daycare surgeries requiring general anaesthesia including general surgical, urological and others surgeries. Patients with known hypertension, ischemic heart disease, neurological problems, psychiatric disease, pregnancy and patients allergic to study drugs were excluded from the study. Ratio (male: female) was computed to present gender distribution. All continuous variables i.e. patient's age, sex, weight, height, body mass index (BMI), and haemodynamic responses i.e. heart rate, arterial oxygen saturation, systolic, diastolic and mean blood pressure and dose of propofol was presented by mean ± standard deviation (SD). Student's t-distribution (unpaired) was used to compare the mean age, weight, height, BMI and dose of propofol. Emergency surgeries, history of gastro esophageal reflux disease, body mass index (BMI) of more than 30 and patients on sedatives or anxiolytics were also excluded from the study. The patients were randomly allocated into two groups; Group A and Group B. Patients in Group A received ketamine-propofol and those in Group B received midazolam-propofol for induction of anaesthesia. Sealed envelope technique was used for randomization. All patients were monitored with Datex Ohmeda S/5 monitor. Electrocardiogram (ECG), noninvasive blood pressure (NIBP), oxygen saturation and end tidal carbon dioxide (ETCO2), were monitored. Baseline blood pressure (systolic and diastolic), and heart rate was taken. Statistical software SPSS 20 was used for data storage and analysis. Chi square test was applied to compare gender and ASA status. P value of <0.05 was considered statistically significant.

III. Result

In our study sixty (60) patients including age, weight and BMI (Table-1). Gender distribution was unequal between the two groups. Group A consisted of 76% males and 24% female patients while, Group B had an equal male and female distribution (Table 2).The mean induction dose was 52.63 (30-120) mg in Group A patients and 51.24 (30-110) mg in Group B patients. The difference between mean inductions doses of propofol were statistically insignificant (P-value of 0.71). Mann Whitney test was also used to compare the mean induction doses of propofol between the two groups, which again showed no statistically significant difference in mean induction doses. of propofol (P-value of 0.52) (Table 3).

Table 1: Demographic Data of Patients including age, weight and BMI.

	Group A		Group B		P-value
	Mean	SD	Mean	SD	
Age	33.84	11.01	37.54	10.85	0.167
Weight	68.78	10.11	65.8	11.45	0.18
BMI	23.17	2.41	23.24	3.41	0.78

Table 2: Demographic Data of Patients.

	Group A	Group B	P-value
ASA I (%)	92.4	72.5	0.038
ASA II (%)	6.8	25.6	

Table 3: Induction dose of Propofol.

	Group A		Group B		P-value
	Mean	SD	Mean	SD	
Induction dose of Propofol	52.63	18.6	51.24	17.55	0.71

IV. Discussion

In co-induction a combination of two sedatives or anaesthetic agents are used for induction of general anaesthesia. The aim is to use a smaller dose of induction agent and thus attain a lower potential for drug related side effects. The desired effect in our study was the achievement of a certain level of sedation and prevention of adverse effects of propofol by giving a combination of two drugs [5]. In this study we determined the induction dose of propofol when it is used in combination with ketamine or midazolam. These drugs were both the groups were similar in their demographic characteristics used as co-induction agents. Each of these drugs has been used as an induction agent for general anaesthesia in their standard doses. All of these agents have certain side effects when they are used alone in their anaesthetic doses. In our study including age, weight and BMI (P=<0.05). Gender distribution was unequal between the two groups. Group A consisted of 76% males and 24% female patients while, Group B had an equal male and female distribution. The mean induction dose was 52.63 (30-120) mg in Group A patients and 51.24 (30-110) mg in Group B patients. Cressey in one study found that pre-treatment with midazolam 0.025 mg.kg-1 produced a significant reduction in propofol dose requirement (mg.kg-1) in both the younger and older age group compared with placebo ($p<0.01$ in both cases) [2]. Hui et al. compared three groups, one group received propofol alone, one ketamine alone and other combination of ketamine and propofol [11]. We found that the induction dose of propofol was reduced in both the groups i.e. ketamine-propofol and midazolam-propofol groups when compared to the recommended induction dose of propofol, although we had not included the propofol alone group. However the difference in the mean induction dose of propofol was statistically insignificant in the ketamine-propofol and the midazolam-propofol group, with a P value of 0.71. It has been proved that the side effects of propofol are directly proportional to the dose of propofol [2]. The lower the dose of propofol, the lesser will be propofol related side effects. In one such study, four groups have been compared in their effects, dose requirements and hemodynamics [12]. They found that using loss of response to verbal commands as end point of induction, the induction dose of propofol was significantly lower in ketamine-propofol and midazolam-propofol groups while higher doses were required in the placebo group. Srivastava U compared placebo-propofol, midazolam-propofol, ketamine-propofol and propofol auto co-induction [12]. There was only a 7% difference between the two groups. The Group Aetamine-propofol was haemodynamically more stable than midazolam-propofol group. We included patients of both sexes and belonging to ASA-I and ASA-II physical status.If we compare our study with the study done by Srivastava [12], they found mean induction dose of propofol of 58 mg (1.2 mg/kg) in ketamine propofol group and 70mg (1.4 mg/kg) in midazolam propofol group. The possible reasons for this insignificant difference might be the gender differences between the two groups. More studies are required in a larger population of patients, and in same gender and comparison between genders to rule out if gender has some effect on the dose requirements of the patients. We should also look for better combinations of induction agents with more haemodynamic stability and less side effects. It was assumed that the group with less propofol requirement would give more stable hemodynamics but this should be studied in different age groups and ASA status.

V. Conclusion

In conclusion, there is no difference in the mean induction dose of propofol with ketamine-propofol and midazolam-propofol co-induction. The possible reasons for this insignificant difference might be the gender differences between the two groups. More studies are required in a larger population of patients, and in same gender and comparison between genders to rule out if gender has some effect on the dose requirements of the patients.

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