

The Induction Dose of Propofol with Ketamine-Propofol and Midazolam-Propofol Co-Induction

Mohsin Nazir Butt* and Aliya Ahmed

North West General Hospital, Pakistan
Aga Khan University Hospital, Pakistan

Abstract

Objective: To determine the mean induction dose of propofol with ketamine-propofol and midazolam-propofol co-induction.

Methods: A total of sixty patients with American Society of Anaesthesiologist (ASA) physical status I and II, aged 20-50 years, of either sex, undergoing daycare surgeries requiring general anaesthesia were included in this study. The patients were randomly allocated into two equal groups. Group K received ketamine-propofol and group M 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 K and 52.33 (30-110) mg in group M. 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: There is no difference in the mean induction dose of propofol with ketamine-propofol and midazolam-propofol co-induction.

Keywords: Co-induction; Ketamine; Propofol; Midazolam

Introduction

Propofol is a commonly used intravenous (IV) induction agent. The induction dose of propofol is 1.5 to 2.5 mg/kg in healthy adults producing unconsciousness, depending upon concomitant medications (i.e. opioid analgesics), the patient's age and physical status, and the extent of surgical stimulation [1]. 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 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 [3]. The objectives of this technique are to improve the ratio of desired versus adverse effects and to reduce the cost of expensive drugs such as propofol [4].

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 [1]. Midazolam has been used as a co-induction agent with Propofol. In one study midazolam propofol co-induction with midazolam dose of 0.025 mg/kg produced a significant reduction in propofol dose requirement in both the younger and older age groups with P value of <0.01(5).

Ketamine is an N-methyl D-aspartate (NMDA) receptor antagonist. It produces dissociative anaesthesia. In contrast to other anaesthetic 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[5].

In this study we plan to determine if co-induction with a small dose of ketamine is a better option compared to midazolam in reducing induction dose of propofol.

Methods

Approval was taken from institutional ethical review committee (ERC) and written informed consent was taken from each patient. It was a randomized double blinded clinical trial, conducted at a tertiary care university hospital over a period of six months.

The patients included in this study were those belonging to American Society of Anaesthesiologist (ASA) physical status I and II, aged 20 to 50 years of either sex, undergoing daycare surgeries requiring general anaesthesia including general surgical, urological and plastic

*Corresponding author: MohsinNazir Butt, MBBS, FCPS (Anesthesia & ICU), North West General Hospital, Peshawar, Khyber pakhtunkhwah, Pakistan; E-mail: mohsin_smcian05@yahoo.com

Received November 03, 2013; Accepted November 28, 2013; Published November 30, 2013

Citation: Butt MN, Ahmed A (2013) The Induction Dose of Propofol with Ketamine-Propofol and Midazolam-Propofol Co-Induction. J Anesth Clin Res 4: 371. doi:10.4172/2155-6148.1000371

Copyright: © 2013 Butt M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

surgeries. Patients with known hypertension, ischemic heart disease, neurological problems, psychiatric disease, pregnancy and patients allergic to study drugs were excluded from the study. 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 K and group M. Patients in group K received ketamine-propofol and those in group M received midazolam-propofol for induction of anaesthesia. Sealed envelope technique was used for randomization. A total of 60 envelopes were prepared, equally for each study group. These envelopes were kept by incharge anaesthesia technician in operating room (or) anaesthesia office. Blinding was done by preparing the study drug in a 5 ml syringe by an anaesthesiologist who was not involved in data collection. Equal volume of 0.3 mg/kg ketamine and 0.03 mg/kg of midazolam were prepared. The study was double blinded, as the patient and anaesthesiologist responsible for assessing the patients were blinded to the study drugs being used. 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. During preoxygenation, all the patients received pethidine 0.8 mg/kg followed one minute later by co-induction agent, either 0.3 mg/kg ketamine or 0.03 mg/kg midazolam. Two minutes after the administration of co-induction agent, each patient received 20 mg of lignocain. Just before injecting propofol each patient was asked to open their eyes and start counting. Injection propofol was given 10 mg every five seconds until patient stopped counting and did 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 (OAA/S) of 2 [6]. It was assessed by prodding the shoulder to see if there was a response. If there was movement on prodding of shoulder, additional boluses of propofol 10mg was given until there was no response. Total dose of propofol was noted to obtain (OAA/S) score of 2. At this point our study was completed. From this point onward, the anaesthesia management was continued as planned for the procedure being performed. A data collection form was used for recording the study observations.

Statistical Analysis

Using one sided alternatives with type I error 0.05 and power 0.80, assuming a percentage change in mean of 20% and percentage coefficient of variation of 40% in dose of propofol between two groups, the calculated sample size is a total of 60 patients equally divided into ketamine-propofol and midazolam-propofol groups.

Statistical software SPSS 15 was used for data storage and analysis. 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. Chi square test was applied to compare gender and ASA status. P value of <0.05 was considered statistically significant. Stratification was done with regards to age, gender, BMI and ASA status to see the effect of them on outcome.

Result

Both the groups were similar in their demographic characteristics

including age, weight and BMI (P=<0.05) (Table 1). Gender distribution was unequal between the two groups. Group K consisted of 80% males and 20% female patients while, group M had an equal male and female distribution (Table 2).

The mean induction dose was 53.67 (30-120) mg in group K patients and 52.33 (30-110) mg in group M patients. The difference between mean inductions doses of propofol 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, which again showed no statistically significant difference in mean induction doses of propofol (P-value of 0.57) (Table 3) (Figure 1).

Discussion

In this study we determined the induction dose of propofol when it is used in combination with ketamine or midazolam. These drugs were

	Group K Mean (SD)	Group M Mean (SD)	Mean difference (95% C.I.)	p-value
Age	32.93 (10.06)	36.63 (10.95)	-3.7 (-9.14-1.74)	0.178
Weight	69.80 (9.89)	66.7 (11.55)	3.03 (-2.52-8.59)	0.28
BMI	24.15 (2.54)	24.17 (3.42)	-0.011 (-1.56-1.54)	0.98

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

	Group K	Group M	P value
ASA I (%)	93.3	73.3	0.038
ASA II (%)	6.7	26.7	

Table 2: Demographic Data of Patients.

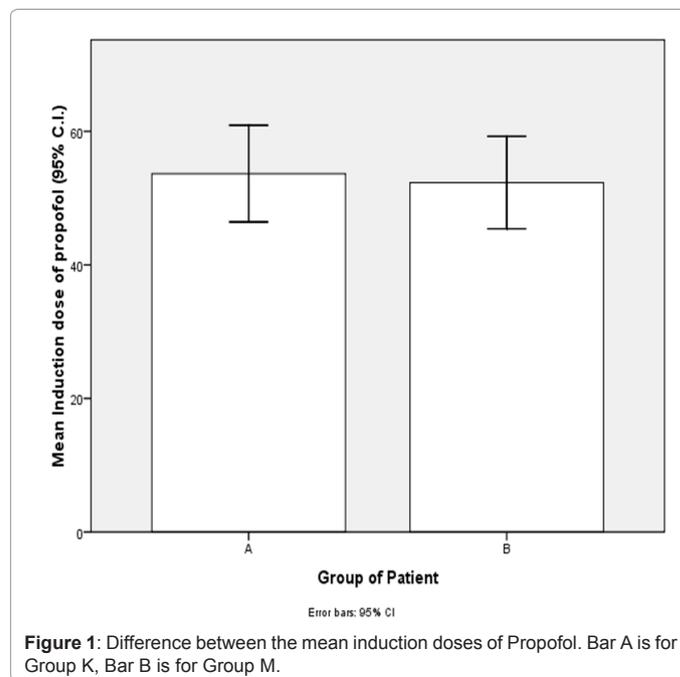


Figure 1: Difference between the mean induction doses of Propofol. Bar A is for Group K, Bar B is for Group M.

	Group K Mean (SD)	Group M Mean (SD)	Mean difference (95% C.I.)	p-value
Induction dose of Propofol	53.67 (19.3)	52.33 (18.51)	1.33 (-8.46-11.12)	0.78

Table 3: Induction dose of Propofol.

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 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 main objectives of this technique are to improve the ratio of desired versus adverse effects and to reduce the cost of expensive drugs such as propofol [1]. 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.

The mean induction dose of propofol when used alone is 1.5-2.5 mg/kg [2]. 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) [5]. Hui et al. compared three groups, one group received propofol alone, one ketamine alone and other combination of ketamine and propofol [7]. At hypnotic end point they found the dose of Propofol to be 1.10 mg/kg in group receiving propofol alone while 0.63 mg/kg in the combination group i.e. ketamine-propofol. The reduction in the dose of propofol in the combination group was statistically significant. 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 0.78. Our objective was to determine the difference in the mean induction dose of propofol when used with ketamine or midazolam and to identify the better co-induction agent, with propofol in terms of reduction of the induction dose of propofol. It has been proved that the side effects of propofol are directly proportional to the dose of propofol [5]. 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 [8]. Srivastava U compared placebo-propofol, midazolam-propofol, ketamine-propofol and propofol auto co-induction [8]. 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. In our study we found a minimal difference in the induction doses of propofol between ketamine-propofol and midazolam-propofol groups which was 1.33 mg with a p-value of 0.78. 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 [8], 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. There was only a 7% difference between the two groups. The group ketamine-propofol was haemodynamically more stable than midazolam-propofol group. In our study the difference in the mean induction dose of propofol was not statistically significant (P value 0.78). 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. In Srivastava's study [8], the decrease in mean blood pressure was maximum in saline propofol (control) group (21%), while it was 13% in midazolam propofol group and minimum in ketamine propofol group (4%) despite the insignificant difference in the mean induction dose of propofol in ketamine propofol and midazolam propofol groups.

The strength of our study is that it was a double blind randomized clinical trial and all the cases were performed by one anesthetist, thus eliminating the observer bias. However the limitation of the study was that the hemodynamic changes between the two groups, i.e. ketamine-propofol and midazolam-propofol were not compared. Hemodynamic stability is an added benefit, which would make a particular co-induction combination more attractive in high risk cardiac patients.

Conclusion

There is no difference in the mean induction dose of propofol with ketamine-propofol and midazolam-propofol co-induction.

Acknowledgements

I am very thankful to following persons for helping me in my study.

Dr. Aliya Ahmed—(Supervisor, Scientific advisor & critical reviewer)

Mr. IqbalAzam—(Statistical Analysis)

Mr. Raza—(Blinding & Data Collection)

References

1. Barash PG, Cullen BF, Stoelting RK, Paul FW, Matthew RE, et al. (2009) *Intravenous Anesthetics: Clinical anesthesia*. (5stedn), Lippincott Williams & Wilkins, Philadelphia, USA.
2. Sebel PS, Lowdon JD (1989) Propofol: a new intravenous anesthetic. *Anesthesiology* 71: 260-277.
3. Win NN, Kohase H, Yoshikawa F, Wakita R, Takahashi M, et al. (2007) Haemodynamic changes and heart rate variability during midazolam-propofol co-induction. *Anaesthesia* 62: 561-568.
4. Anderson L, Robb H (1998) A comparison of midazolam co-induction with propofolpre dosing for induction of anaesthesia. *Anaesthesia* 53: 1117-1120.
5. Cressey DM, Claydon P, Bhaskaran NC, Reilly CS (2001) Effect of midazolam pretreatment on induction dose requirements of propofol in combination with fentanyl in younger and older adults. *Anaesthesia* 56: 108-113.
6. Gürses E, Sungurtekin H, Tomatir E, Dogan H (2004) Assessing propofol induction of anesthesia dose using bispectral index analysis. *AnesthAnalg* 98: 128-131, table of contents.
7. Hui TW, Short TG, Hong W, Suen T, Gin T, et al. (1995) Additive interactions between propofol and ketamine when used for anesthesia induction in female patients. *Anesthesiology* 82: 641-648.
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: 112-114.