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A comparative study on measure the efficacy of midazolam in reducing the dose of propofol in co induction: A double blind ranadomized trial

Dr. Zameeruddin[1*], Dr. Syed Ahamed Peerzade[2]

[1] Associate Professor, Department of Anaesthesia, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

[2] Post Graduate, Department of Anaesthesia, Shadan Institute of Medical Sciences, Hyderabad, Telangana, India

Abstract

Priming principle refers to administration of a subanaestheic dose of an agent prior to its actual anaesthetic dose. Propofol is an effective substitute to midazolam for intravenous induction. The aim of the present study was to evaluate the efficacy of priming technique in relation to induction agents. Clinical efficacy in terms of dose reduction and alteration in peri-intubation haemodynamics was compared in midazolam induction and midazolam Propofol co-induction groups along with a control group. The study was carried out in 30 patients scheduled for general surgery, who were randomly divided into two equal groups. Group I received. Midazolam 0.05 mg/kg BW (20% of the pre-calculated induction dose), group II received 0.05 mg/kg normal saline. This was followed by induction with Propofol 2 minutes later in all the two groups at a predetermined rate till the bispectral index value of 45 was attained. The demographic data were comparable for age, weight and sex in both the groups. Total patients were divided into two groups with 30 patients each. It was observed that total induction dose of Propofol was significantly decreased in the study group 95 mg compared to control group 155.6 mg. Heart rate was better maintained in study group with minimal post-intubation response. The values of systolic, diastolic and mean blood pressure observed at 1 min after induction also showed significant decrease in control group compared to study group.

Conclusions: Propofol produces smooth, rapid, pleasant and safe induction. Priming with Propofol can be practiced due to its cost effectiveness and better haemodynamic profile and safety. The results showed a significant decrease in induction dose requirement in both the groups but haemodynamic stability during induction and intubation was more in Propofol auto-co-induction group.

Keywords: midazolam, propofol, auto-co-induction, bispectral index

Introduction

A primary goal for ambulatory anesthesia is rapid recovery from anesthesia leading to rapid patient discharge with minimal side effect [1]. Delayed or complicated recovery from general anesthesia can have a considerable impact on patient safety, patient satisfaction, recovery room resources, and cost of patient care. Post-operative pain, nausea and vomiting are common causes for delayed patient discharge and un-planned hospital admission [1]. Faster recovery and reduction of time spent in the post anesthesia care unit (PACU) and ambulatory surgery unit (ASU) can accelerate operating room turn over and reduces cost.

"Co-induction" [5-7] is defined as the concurrent administration of two or more drugs that facilitate induction of anaesthesia documenting *synergism* [7]. However, there is a paucity of studies [3] documenting the application of priming principle in induction agents. Induction agent, Propofol has a good safety record, but relatively expensive. This technique, in relation to induction agents, aims at utilising the sedative, anxiolytic and amnesic properties at sub-hypnotic dosage of induction agent when given a few minutes prior to induction. This study was also done to evaluate whether the priming technique reduces the effective dose of induction agent and favourably influences the periintubation haemodynamics. Propofol and midazolam is a commonly used combination for induction and it shows synergistic interaction for hypnosis and reflex sympathetic suppression [7].

Materials and Methods

Study design

Double blind randomized control trial.

Study setting

Department of Anesthesiology, SIMS, Hyderabad.

Study duration

1 year-from August'16 to August'2017

Study population

Patients who were posted for elective surgical procedures under general anesthesia who satisfied inclusion and exclusion criteria.

Inclusion criteria

1. ASA grade I and 2.
2. Age group 18-50 years
3. Elective surgical procedures under general anaesthesia.

Exclusion criteria

1. Chronic use of hypnotics and analgesics.

2. Abnormal body weight (more than 20% difference from normal BMI).
3. Epileptics on treatment with phenytoin.
4. Pregnant and lactating.
5. Patients allergic to study medications.
6. Uncorrected hypotension.
7. Patients with liver disease.

Sample size

Samples were from adult cases posted for elective surgical procedures in Shadan Institute of Medical Sciences, Hyderabad. All who were posted for elective surgical procedures under general anesthesia and who met inclusion criteria were selected until the sample size calculated was obtained. It was estimated that a minimum of 28 patients in each group would be required to have a 92% power to detect a significant difference in the duration with 95% confidence interval. Calculating for any dropouts in the study a total of 30 patients were taken in each group.

Procedure

Approval from research methodology and ethical committee of Shadan Institute of Medical Sciences, Hyderabad obtained prior to the study. Written informed consent obtained. The patients posted for elective surgical procedures that satisfied the inclusion and exclusion criteria and those who gave written informed consent were allocated randomly into 2 groups using a computer generated random table.

All patients included in the study underwent a detailed pre anesthetic check- up. Age and body weight were noted. Patients were kept fasting for 6 hours prior to surgery. Patients were given Tab. Ranitidine 150 mg and Tab. Alprazolam 0.25mg on the pre-operative day at night and on the day of surgery at 6:30 am ECG, pulse oxymeter and non-invasive blood pressure monitors were attached. Baseline heart rate and mean arterial blood pressure were noted. After attaining intravenous access Inj. Glycopyrrolate 0.04mg/kg body weight, Inj. Ondansetron 4 mg and Inj. Fentanyl 1 microgram/kg BW were given. After pre oxygenation.

- **Group A:** Received Inj. Midazolam 0.05 mg/kg BW (0.05 ml/kg BW).
- **Group B**: Received 0.05ml/kg BW normal salin

This was followed 2 minutes later by aniv induction with propofol at a rate of 30 mg/10 seconds till the loss of verbal response and motor response was attained. Subsequent muscle relaxation was attained by succinyl choline 2 mg/kg and anesthesia maintained with nitrous oxide, oxygen (4:2), and iso flurane. Vecuronium is used for muscle relaxation as maintenance.

Blinding in the present study

Patient was blinded as the drug is given during sleep. The drugs were administered by anesthesiologist in charge of the OT who was unaware of the purpose of the study. The outcome was measured by the investigator.

Outcome measure

1. Total dose of propofol in mg/kg body weight required in achieving loss of verbal response and loss of motor response.
2. Mean arterial blood pressure and heart rate were measured just before induction, 1 minute after induction, just before intubation, immediately after intubation and 5 minutes after induction.

Statistics

The data were collected with the help of a prestructrual proforma. Analysis was done using Epi info version 7. Comparison between the groups for induction dose and haemodynamic parameters was done using mann-whitney/wilocoxon two-sample test (Kruskal-Wallis test for two groups) as the observation did not follow a normal distribution.

Results

Comparison of Demographic Data

Age, weight and gender distribution were comparable for Group A and Group B (p value >0.05).

Table 1: Distribution of samples according to age

Age	Group A		Group B	
	Count	Percent	Count	Percent
20-34	15	50	13	43.3
35-49	15	50	16	53.3
>50	0	0	1	3

As shown in Table 2, the mean age of patients in Group A was 36.3 (±10.2) whereas that in Group B was 35.8 (±8.1), with a p-value of 0.92. Hence the differences in age between both the groups were not statistically significant as p value is >0.05. The mean body weight in Group A was 61 (±7.5) and that in Group B was 77.2 (±8.8) with a p-value of 0.63. Hence the differences in body weight between both the groups were not statistically significant as p-value is > 0.05

Table 2: Comparison of sample based on sex

Sex	Group A		Group B		P value
	Count	Percent	Count	Percent	
Male	16	53.33	16	53.33	
Female	14	46.67	14	46.67	0.6

Regarding the distribution of sex (Table 4), in Group A and Group B 53.33% were males and 46.67% are females; (p-value >0.05 and so the difference is statistically insignificant). Hence the demographic data were comparable for age, weight and gender.

Comparison of dose

The mean induction dose of Propofol was 95±16.8 in group A compared to (22.6) in group B as shown in table (p-value < 0.01). Hence there is significant reduction in dose requirement in Group A, compared to Group B.

Table 3: Comparison of dose of propofol

Group	Mean dose of propofol in mg	SD	P value
A	95	16.8	<0.01
B	155.6	22.6	

Comparison of the effect on heart rate

Table 4: Comparison of heart at baseline le**vel**

Group	Mean	SD	P value
A	89.4	9.0	0.34
B	91.1	14.4	

The baseline heart rates were comparable.

Table 5: Comparison of heart rate at different time intervals

Time	Group A		Group B		P value
	Mean	SD	Mean	SD	
Before induction	89.4	9.0	91.1	14.4	0.34
1 min after induction	81.8	6.8	80.8	12.0	0.86
Just before intubation	82.0	5.6	80.6	12.9	0.65
Immediately after intubation	95.4	9.98	100.6	15.5	0.065
5 min after induction	87.3	12.0	84.5	10.9	0.98

Discussion

Day surgery is a cost-effective, quality approach to surgery that has expanded rapidly in recent years. The advantages of day case surgeries are mainly to patient and hospital. They include minimal psychological disturbances for the patient especially children, economical with reduced requirement of nursing and medical supervision and also advantage to hospital services allowing more number of patients to be treated and finally consequent reduction in the risk of hospital-acquired infection and venous thrombo-embolism (VTE) [5, 6].

Shorter acting anaesthetic agents e.g. Propofol and monitors e.g. BIS (bispectral array) and EEG have been used which significantly reduces the hospital stay. If BIS is maintained between 45-65, lesser anaesthetics are required without intra-operative awareness with faster recovery and reduced postoperative complications thus early hospital discharge.

Induction of anesthesia is one of the important events in the conduct of general anesthesia. Propofol is now the commonest induction agent used in anesthesia. Methods which can decrease the dose requirements of the drug may be helpful in reducing the side effects and also the cost.

In our study we evaluated whether midazolam conduction applied for induction dose of propofol would affect the total induction dose requirement of propofol and thereby reduce the associated haemodynamic changes.

In our study the demographic data were comparable for age, weight and sex in both groups. (P-value >0.05). Mean induction dose of propofol was 95+16.8 Group A, who received midazolam co-induction, compared to 155.6+22.6 in group B patients, who received only propofol. We observed a 38.94% reduction in induction dose requirement of propofol by applying the midazolam co-induction technique.

The mechanisms involved in co-induction are poorly understood, it has been suggested that co-induction results from a combination of both pharmaco dynamic interactions at a receptor level [16, 17] and pharmacokinetic effects related to the distribution of the induction agent [15, 16]. Anderson and Robb [15] proposed a pharmacokinetic theory that part of the mechanisms of action of co-induction drugs is to reduce anxiety and the associated sympathetic response. Midazolam produces anxiolytic when administered pre-induction and this mechanisms may, by reducing cardiac output, help prevent rapid distribution of propofol in young anxious patients.

Other arguments for co-induction of anesthesia include cost [8, 14] Propofol 1% for induction of anesthesia is currently supplied as a 200 mg ampoule for single patient use. The cost is around rupees 200. A second ampoule of propofol is less likely to be required in younger patients. The cost of midazolam 5 ml vial is only about rupees 30. So there is definite economic benefit to the patient.

A similar study was conducted by Short TG *et al* [9]. They studied interactions between i.v., propofol and midazolam for induction of anesthesia in 200 UN premedicated female patients undergoing elective gynaecological surgery. For hypnosis, synergistic interaction was found p less than 0.01), the combination having 1.44 times the potency of the individual agents. Although midazolam failed to produce anesthesia in the dose range used, the dose of propofol required to produce anesthesia was reduced by 52% in the presence of midazolam ($P < 0.01$). The reduction in arterial pressure at induction was the same for the combination as for the individual agents. The results obtained in our study were in accordance with this. But the reduction in the dose of propofol was 38.9% compared to 52% in the above mentioned study. This may be due to the difference in premedication. In our study subjects in both the groups were given inj. Fentanyl before induction, whereas, the above mentioned study was done on unpremeditated patients.

Lai HC *et al* got a result similar to that of ours. Lai HC *et al* [10] conducted a study to evaluate the co-administration of midazolam and propofol during anesthesia for endoscopic microsurgery and test its influences on the consumption of propofol and the quality of anesthesia. Forty-two patients receiving selective endoscopic microsurgery were enrolled in this study. They found that co-administration of midazolam and propofol in TIVA could reduce the induction dose and the total dose of propofol by 51% and 25% respectively but still achieve the same anesthetic effects. Vital signs and recovery were not influenced, and incidences of adverse effects did not increase. This is in harmony with our study. But the reduction in dose is 51% when compared to 38.9% in our study.

We also evaluated, whether applying midazolam co-induction technique would affect the associated hemodynamic parameters. The heart rates at various intervals were comparable. The MAP was also comparable. From this we concluded that the hemodynamic parameters were unaffected by propofol midazolam co induction. This is in accordance with the studies conducted by Short TG *et al*, Lai HC *et al*, Cressy *et al* [11] Anderson *et al* [8] and Roopam Kataria *et al* [12].

These observations point that although midazolam co-induction significantly reduces the induction dose of propofol, it does not provide haemodynamic stability in peri-intubation period. Similar results were also obtained by Cressy *et al* [11]. Where significant dose reduction in propofol was found in

midazolampre-treatment group but there were no demonstrable benefits in terms of cardiovascular stability.

Conclusion

This study was done to evaluate the efficacy of midazolam as conduction in reducing the induction dose of propofol during induction of general anesthesia. 60 patients belonging to the American Society of Anesthesiology (ASA) physical status classification class I & II, of either sex, between 18-50 years, scheduled for elective surgeries under general anesthesia were. Divided randomly into two groups each consisting of 30 patients. We observed a 38.9% reduction in the dose requirement of propofol in group A. the haemodynamic parameters were comparable in both groups.

Based on the results obtained in this study, it can be concluded that co induction with Midazolam reduces the induction dose requirements of propofol with no significant difference in the peri-intubation haemodynamics. Hence co-induction with Midazolam is an effective and safe method to reduce the dose requirement of Propofol during induction of general anesthesia.

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