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STUDY OF EFFICACY OF PROPOFOL AUTO-CO-INDDUCTION VERSUS MIDAZOLAM-PROPOFOL CO-INDUCTION USING THE PRIMING PRINCIPLE BY BISPECTRAL INDEX ANALYSIS, A PROSPECTIVE OBSERVATIONAL STUDY

Transfusion Medicine

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ABSTRACT

Background: Auto-co-induction is also known as "Priming technique". It is the technique of giving a pre-calculated dose of induction agent prior to giving full second large dose of the same inducing agent. This technique, in relation to inducing agents, aims at utilizing the sedative and anxiolytic properties at sub-hypnotic dosage of induction agent when given a few minutes prior to induction. Propofol and midazolam is a commonly used combination for induction and it shows synergistic interaction for hypnosis and reflex sympathetic suppression. Midazolam has shown to reduce the dose of propofol required to induce anesthesia by up to 50% without affecting the recovery profile when used as co-induction.We aimed to study priming principle in relation to induction agent Propofol either by co-induction using midazolam or auto-co-induction by Propofol itself with BIS guided anesthesia administered to all patients. **Methods:** Study was conducted on seventy patients. Before induction heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure was noted by the attending anesthesiologist. Patients either received 0.5mg/kg IV Propofol or Midazolam 0.05mg/kg IV as priming dose by the attending anesthesiologist. Patients receiving Propofol as priming agent (Propofol-Propofol Group) were induced with Inj Propofol 2mg/kg IV after 3 minutes by the attending anesthesiologist till BIS value reached to 45-50 (speed of injection was 30mg/10 sec) and loss of response to verbal commands occurred. Patients receiving Midazolam as priming agent (Midazolam-Propofol Group) were induced with Inj Propofol 2mg/kg IV after 3 minutes by the attending anesthesiologist till BIS value reached to 45-50 (speed of injection was 30mg/10 sec) and loss of response to verbal commands occurred. **Results:** Age, weight, duration of surgery, priming dose of midazolam or propofol according to weight of the patients, induction dose of propofol to achieve BIS value of 45-50, total dose requirement of Propofol, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, oxygen saturation and Richmond agitation sedation score at various intervals were noted. The mean total dose requirement of Propofol (mg) in group PP was 118.40 with standard deviation of 15.25 and mean total dose requirement of Propofol in group MP was 77.6 with standard deviation of 9.2. There was statistically significant difference in mean total dose requirement of Propofol between the twogroups with more reduction in Propofol-Midazolam co-induction group as compared to Propofol auto-co-induction group (p value=0.001). **Conclusion:** By using priming principle and BIS guided anaesthesia we can discharge the patients early in propofol auto-co-induction group, while it is delayed in propofol-midazolam group.

KEYWORDS

Propofol, Midazolam, BIS, induction, priming technique.

INTRODUCTION

A primary goal for anesthesia is rapid recovery from anesthesia leading to rapid patient discharge with minimal side effects[1]. Faster recovery and reduction of time spent in the post anesthesia care unit (PACU) can accelerate operating room turn over and reduce cost. 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.Induction of anesthesia can be considered as one of the most crucial events in anesthesiology as it is associated with number of alterations in hemodynamic and physiology of various body systems[2]. Unusual and prolonged hospital stay due to anesthetic drugs definitely increases economic burden and risk of hospital acquired complications.Propofol is a preferred induction agent nowadays due to its properties of smoother and more rapid induction, rapid awakening and orientation times, clear headed recovery, decreased incidence of post-operative nausea, vomiting and better intubating conditions[3,4]. Major disadvantage of rapid induction with propofol is the considerable dose dependent decrement in the systemic arterial pressure, primarily due to reduction in cardiac output and systemic vascular resistance[5]. It has a good safety record but when used as the sole induction agent it causes significant decrease in arterial blood pressure[6,7] and cardiac output[8,9].

Various methods to reduce the induction dose of propofol, like concurrent use of nitrous oxide, opioids, barbiturates like thiopentone, benzodiazepines like midazolam, clonidine, augmentation with local anesthetics, magnesium sulphate and use of "auto- co-induction have been proposed[10,11]. In order to balance the ratio of desired versus adverse effects and decrease the costs, the concept of co-induction got attraction. Auto-co-induction is also known as "Priming technique". It is the technique of giving a pre-calculated dose of induction agent prior to giving full second large dose of the same inducing agent[12]. This technique, in relation to inducing agents, aims at utilizing the sedative and anxiolytic properties at sub-hypnotic dosage of induction agent when given a few minutes prior to induction[12].

The technique of co-induction using two or more agents to induce anesthesia has been studied in recent years. When induction agent like Propofol is combined with a sedative benzodiazepine, Midazolam, a synergism occurs between these two drugs causing reduction in total dose of primary drug like Propofol, a technique called co-induction[13]. Synergism has been reported between a number of induction agents and midazolam[14,15,16,17]. The potential benefits of synergism in clinical practice would mean that anesthesia could be induced with a smaller combined total dose of anesthetic agents with fewer side effects.Midazolam in small amounts (0.1 mg/kg) causes relatively little cardiac or respiratory depression. By premedication with low doses of midazolam, it is hoped that the reduction in propofol induction dose requirement afforded by the synergistic interaction for hypnosis would reduce the incidence of adverse cardiovascular and respiratory effects. A number of studies have examined the induction qualities of the combination of midazolam, propofol and an opioid in fit young adult populations[15,16,17] and in children[18].Propofol and midazolam is a commonly used combination for induction and it shows synergistic interaction for hypnosis and reflex sympathetic suppression. Midazolam has shown to reduce the dose of propofol required to induce anesthesia by up to 50% without affecting the recovery profile when used as co- induction[13,15].Propofol and midazolam is a commonly used combination for induction and it shows synergistic interaction for hypnosis and reflex sympathetic suppression. Midazolam has shown to reduce the dose of propofol required to induce anesthesia by up to 50% without affecting the recovery profile when used as co- induction[13,15].

Bispectral index is a derived electroencephalographic parameter that has been extensively validated as a monitor of depth of anesthesia .BIS is a multiprocessor EEG parameter developed to measure the effects of anesthetics on brain hypnotic state, making it possible to measure the

depth of anesthesia. The introduction of the BIS in clinical practice is a reliable method to assess brain function and allows the titration of hypnotics on cortical activity. BIS values in the range of 40-60 are recommended as indicators of adequate depth of general anesthesia and may be used to guide titration of general anesthesia instead of routine clinical signs[19]. Tong J et al concluded from a study that titrating propofol with BIS monitoring during balanced anesthesia decreased propofol use and significantly improved recovery. These findings indicate that the use of BIS may be valuable in guiding the administration of propofol intraoperatively[20].

AIMS AND OBJECTIVES

1. To evaluate the application of priming principle for the induction dose of propofol.
2. To evaluate the effect of priming principle on peri-intubation hemodynamics.
3. To compare the recovery criteria in propofol auto-co-induction and midazolam-propofol co-induction.

MATERIAL AND METHODS

The present prospective observational study was conducted at Sher-i-Kashmir Institute of Medical Sciences, Srinagar from November 2021 to March 2023, after approval from institutional ethical committee on ASA I and II physical status, aged 18-55 years, undergoing surgical procedures under general anaesthesia over a period of 2 years.

Inclusion Criteria

- ASA Class 1 and 2
- Adult patients aged 18 to 55

Exclusion Criteria

- Patient Refusal.
- Patient less than 18 years old.
- Patients with history of allergy to above medications, anticipated difficult intubation.
- History of cardiac, pulmonary, hepatic or renal disease, or significant obesity (BMI>30).

Study was conducted on seventy patients. Before induction heart rate, systolic blood pressure, diastolic blood pressure and mean arterial blood pressure was noted by the attending anesthesiologist. Patients either received 0.5mg/kg IV Propofol or Midazolam 0.05mg/kg IV as priming dose by the attending anesthesiologist.Patients receiving Propofol as priming agent (Propofol-Propofol Group) were induced with Inj Propofol 2mg/kg IV after 3 minutes by the attending anesthesiologist till BIS value reached to 45-50 (speed of injection was 30mg/10 sec) and loss of response to verbal commands occurred. Patients receiving Midazolam as priming agent (Midazolam-Propofol Group) were induced with Inj Propofol 2mg/kg IV after 3 minutes by the attending anesthesiologist till BIS value reached to 45-50 (speed of injection was 30mg/10 sec) and loss of response to verbal commands occurred.

After neuromuscular blockade to facilitate oral endotracheal intubation, anaesthesia was maintained with oxygen, nitrous oxide and isoflurane using close circle absorber system with IPPV mode (intra-operatively BIS was maintained between 40-60). Analgesia was provided with fentanyl 2mcg/kg iv slowly in all patients. Following doses were calculated:

I) Priming dose of midazolam or propofol according to weight of the patients.
II) Induction dose of propofol to achieve BIS value of 45-50.
III) Total dose requirement of Propofol.

Intra operative monitoring:

I. Intraoperatively, Pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, oxygen saturation and BIS value were recorded at post priming interval, immediately after induction, immediately after intubation, 5 minutes and 10 minutes after intubation.
J. Duration of surgery was noted.

Post-operative monitoring:

Following parameters were observed at every 15 min interval for 1 hour and then at 90 minutes and 120 minutes.

1) Pulse rate
2) Systolic blood pressure, diastolic blood pressure, mean arterial blood pressure
3) Oxygen saturation
4) Richmond agitation sedation score.

Richmond Agitation Sedation Scale (RASS)[42,4]

+ 4	Combative, violet, danger to staff
+ 3	Pulls or removes tube(s) or catheters; aggressive
+ 2	Frequent non purposeful movement, fights ventilator
+ 1	Anxious, apprehensive, but not aggressive
0	Alert and calm
- 1	Awakens to voice (eye opening/contact) > 10 seconds
- 2	Light sedation; briefly awakens to voice (eye opening/contact) < 10 seconds
- 3	Moderate sedation; movement or eye opening. No eye contact
- 4	Deep sedation; no response to voice, but movement or eye opening to physical stimulation
- 5	Unarousable; no response to voice or physical stimulation

RESULTS

The present study was undertaken to evaluate the application of priming principle for the induction dose of propofol, to evaluate the effect of priming principle on peri-intubation hemodynamics and to compare the recovery criteria in propofol auto co-induction and midazolam-propofol co-induction. Two groups of 35 patients each were randomly selected for this study: Patients either received 0.5mg/kg Propofol or Midazolam 0.05mg/kg IV as priming dose by the attending anesthesiologist.

After 3 minutes of priming, all patients were induced with Inj Propofol 2mg/kg IV by the attending anesthesiologist till BIS value reached to 45-50 (speed of injection was 30mg/10 sec) and loss of response to verbal commands occured. Following data was collected and analyzed statistically;

1. Age, weight, duration of surgery,priming dose of midazolam or propofol according to weight of the patients, induction dose of propofol to achieve BIS value of 45-50,total dose requirement of Propofol, heart rate, systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, oxygen saturation and Richmond agitation sedation score at various intervals were noted.
2. The groups were comparable with respect to age, weight and height.
3. There was statistically no significant difference between the two groups with respect duration of surgery.
4. There was statistically significant difference in the mean induction dose of propofol to achieve BIS value 45-50 between two groups with greater reduction in the induction dose of propofol to achieve BIS value of 45-50 in group MP as compared to group PP.(Table 1)
5. There was statistically significant difference in the mean total dose requirement of Propofol with greater reduction in the total dose requirement of Propofol in group MP as compared to group PP.
6. There was statistically significant difference in mean heart rate in two groups post induction and post intubation. Patients in group PP had greater fall in mean heart rate as compared to group PP. Post intubation more rise in mean heart rate was observed in group MP. Rest of the time no statistically significant change in heart rate was observed.
7. There was statistically significant difference in mean SBP, DBP and MAP between two groups post intubation with higher mean SBP, DBP and MAP in group MP as compared to group PP. Rest of the time the difference between the groups with respect to SBP, DBP and MAP was statistically insignificant.
8. The statistically significant difference in mean BIS value was observed between the two groups post priming and post induction. Post priming maximum reduction in BIS value was observed in the group PP as compared to group MP which was statistically significant, post induction maximum reduction in BIS value was observed in group PP as compared to group MP which was statistically significant. Rest of the time the difference was statistically insignificant.

Postoperatively the mean Richmond Agitation Sedation Score (RASS) score in group MP was statistically significantly high upto 60 minutes as compared to group PP. After 90 minutes there was no statistically significant differences between two groups with respect to mean Richmond Agitation Sedation Score (RASS) sco

Table 1: Comparison based on mean induction dose of Propofol to achieve BIS value of 45-50 in two groups

Group	N	Mean	SD	95% CI	P-value
Group PP	35	85.4	11.90	81.3-89.5	
Group MP	35	77.6	9.27	74.4-80.8	

***Statistically Significant Difference (P-value<0.05); CI: Confidence Interval**

DISCUSSION

The mean induction dose of Propofol (mg) to achieve BIS value of 45-50 in group PP was 85.4 with standard deviation of 11.90 and mean induction dose of Propofol to achieve BIS value 45-50 in group MP was 77.6 with standard deviation of 9.27. There was statistically significant difference in mean induction dose ofPropofol to achieve BIS value 45-50 between the two groups with greater reduction in group MP as compared to group PP (p value=0.003). Our results are in concordance with Dr. Krupali et al "A study of propofolauto-co-induction versus midazolam co-induction using priming principle bybispectral index analysis for ambulatory surgery" who in their study observed that the induction dose of Propofol to achieve BIS value between 45-50 during induction was decreased in both the study groups but more reduction was seen in midazolam co-induction group (p value<0.005)[21].

The mean total dose requirement of Propofol (mg) in group PP was 118.40 with standard deviation of 15.25 and mean total dose requirement of Propofol in group MP was 77.6 with standard deviation of 9.2. There was statistically significant difference in mean total dose requirement of Propofol between the twogroups with more reduction in Propofol-Midazolam co-induction group as compared to Propofol auto-co-induction group (p value=0.001). Our results are in concordance with Anderson L,Rob H et al, "A comparison of midazolam co-induction with propofol predosing for induction of anaesthesia"who in their study observed that the dose of Propofol to induce anaesthesia was significantly less in patients in the midazolam group (1.71mg/kg) than the Propofol group(1.87mg/kg)[22]. Our results are in concordance with Djaiani G et al "Propofol auto-co-induction as an alternative to midazolam co-induction for ambulatory surgery"who in their study observed significant reduction of the total induction dose of Propofol as much as 40% in MP group as compared to 23% reduction in PP group[23]. Our results are in concordance withRohit Chobhe et al "A comparativestudy of efficacy of Propofol Auto co induction versus midazolam co induction using the priming principle" who in their study observed that priming with both, midazolam and Propofol is effective in reducing the dose of propofol induced anaesthesia with more significant reduction in midazolam group[24].

Baseline heart rate in group PP was 83.37 with standard deviation of 9.57 and in group MP was 81.17 with standard deviation of 9.63. The baseline heart rate was comparable in both the groups and statistically not significant (p value=0.126). The statistically significant difference in heart rate was observed between the two groups post induction and post intubation. Post induction, patients in group PP had higher fall in mean heart rate (70.14±8.25) as compared to group MP (76.91±9.10) which was statistically significant (p value=0.002).Post intubation, there was rise in heart rate in both the groups but least rise was observed in the group PP (86.17±9.51) as compared to group MP (94.20±11.88) which was statistically highly significant (p value=0.001). Rest of the time no significant change in mean heart rate was observed. Our results are in concordance with Win NN et al "Hemodynamic changes and heart rate variability during midazolam-propofol co-induction"who in theirstudy observed that mean heart rate after tracheal intubation was significantly increased(p value=0.001) in the midazolam-propofol co-induction group[25]. Our results are in concordance with Kataria et al "A comparative study ofefficacy of propofol auto -co-induction versus midazolam co-induction using thepriming principle" who in their study observed that mean heart rate after induction decreased more in group PP as compared to group MP which was statistically highly significant (p value<0.001) and after intubation mean heart rate increased in both the groups with less rise in Propofol auto -co-induction group which was statistically highly significant(p value<0.001)[26].

Rise in mean arterial pressure after intubation in both the groups was due to stress response produced by laryngoscopy and endotracheal intubation. But lesser rise in MAP was observed in group PP, which was due to reduction in the sympathetic drive and cardiac output. Propofol pre-treatment does not completely attenuate reflex sympathetic stimulation secondary to intubation, but it is definitely more advantageous than group MP. Baseline mean SBP (mmHg) in group PP was 125 with standard deviation of 11.68 and in group MP was 123.49 with standard deviation of 8.90. The baseline mean SBP was comparable in both the groups and statistically not significant (p value=0.485).The statistically significant difference in mean SBP was observed between the two groups post intubation. Post intubation, least rise in SBP was observed in the group PP (129.09±10.86) as compared to group MP (134±10.31) which was statistically significant (p value=0.023). Rest of the time the difference wasstatistically insignificant.

Baseline mean DBP (mmHg) in group PP was 75.49 with standard deviation of 7.09 and in group MP was 74.80 with standard deviation of 7.22. The baseline mean DBP was comparable in both the groups and statistically not significant (p value=0.691).The statistically significant difference in mean DBP was observed between the two groups post intubation.Post intubation,least rise in DBP was observed in thegroup PP (78.34±9.84) as compared to group MP (82.77±5.76) which was statistically significant (p value=0.024). Rest of the time the difference was statistically insignificant. Baseline mean MAP (mmHg) in group PP was 92.07 with standard deviation of 8.14 and in group MP was 91.03 with standard deviation of 7.44. The baseline mean MAP was comparable in both the groups and statistically notsignificant (p value=0.578). The statistically significant difference in mean MAP was observed between the two groups post intubation .Post intubation, least rise in MAP was observed in the group PP (95.26±9.88) as compared to group MP (100.17±7.53) which was statistically significant (p value=0.019). Rest of the time the difference was insignificant.

Our results are in concordance with Dr. Krupali et al "A study of propofolauto-co-induction versus midazolam co-induction using priming principle bybispectral index analysis for ambulatory surgery" who in their study observed that immediately post intubation there was rise in systolic, diastolic and mean arterial blood pressure in both the groups but least rise was observed in group PP which was statistically significant[21]. Our results are in concordance with Kataria et al "A comparative study of efficacy of propofol auto-co-induction versus midazolam co-induction using thepriming principle" who in their study observed that immediately post intubation there was rise in systolic,diastolic and mean arterial blood pressure in both the groups but least rise was observed in group PP which was statistically significant. Rest of the times there was statistically no significant differences between two groups at various intervals[26]. Similar results were obtained by the study done byChobhe R et al"A comparative study of efficacy of Propofol Auto co induction versus midazolam co induction using the priming principle" who in their study observed that that immediately post intubation there was rise in systolic,diastolic and mean arterial blood pressure in both the groups but least rise was observed in group PP which was statistically significant. Rest of the times there was statistically no significant differences between two groups at various intervals[24].

Baseline mean BIS value in group PP was 99.37 with standard deviation of 0.84 and in group MP was 99.31 with standard deviation of 0.83. The baseline mean BIS value was comparable in both the groups and statistically not significant (p value=0.776).The statistically significant difference in mean BIS was observed between the two groups post Priming and post induction. Post priming maximum fall in BIS value was observed in the group PP (73.71±6.71) as compared to group MP (76.29±5.34) which was statistically significant (p value=0.043). Post induction maximum reduction in BIS value was observed in group PP (48.13±1.86) as compared to group MP(49.57±2.71) which was statistically significant(p value=0.012). Rest of the time the difference was statistically insignificant.

Our results are in concordance withDr. Krupali et al "A study of propofolauto-co-induction versus midazolam co-induction using priming principle by bispectral index analysis for ambulatory surgery" who in their study observed that maximum fall in mean BIS value post priming and post induction were noted in group PP as compared to group MP. Thereafter no statistically significant change was observed in BIS value[21].

Similar results were obtained Gurses E et al "Assessing propofol induction ofanaesthesi dose using bispectral index analysis" who in their study observed that dose of Propofolassessed by BISanaly sis result edinanimportantreductionofPropofol requirement[27]. Similar

results were obtained by Punjasawadwong Y et al "Bispectralindex for improving anaesthetic delivery and postoperative recovery" who in their study observed that anaesthesia guided by BIS kept within the recommended range improves anaesthetic delivery and reduced the requirement for Propofol and volatile anaesthetics[28]. Our observations also correlate with Wang D et al "Bispectralindex monitoring of the clinical effects of propofol closed-loop target-controlledinfusion" who in their study observed closed loop systems under bispectral index anaesthesia depth monitoring reduced the dose of Propofol[29]. Postoperatively the mean Richmond Agitation sedation score (RASS) in group PP after 15 minutes was -2.20 with standard deviation of 0.76 and in group MP was -3.60 with standard deviation of 0.85 which was higher in group MP as compared to group PP and was statistically significant (p value<0.001). Mean Richmond Agitation sedation score (RASS) after 30 minutes in group PP was -1.37 ±0.55 and in group MP was - 2.34±0.48 which higher in group MP as compared to PP and was statistically significant (p value<0.001). Mean Richmond Agitation sedation score (RASS) after 45minutes in group PP was -0.91 ±0.28 and in group MP was -1.57±0.50 which was higher in group MP as compared to group PP and was statistically significant (p value<0.001). Mean RASS after 60 minutes in group PP was 0.00 ±0.00 and in groupMP was -0.83 ±0.38 which higher in group MP as compared to group PP and WAS statistically significant (p value<0.001). After 90 minutes there was no statisticallysignificant differences between two groups.

Our results are in concordance with Djaiani G et al "Propofol auto-co-induction as an alternative to midazolam co-induction for ambulatory surgery"who in their study observed postoperative recovery was delayed in Midazolam co-induction group[23].Our results are in concordance with Sang Hyun Kwak et al "Comparison ofIntravenous Propofol and Midazolam Anaesthesi for Outpatient Cystoscopy" whoin their study observed that postoperative recovery was faster in Propofol than inMidazolam group[30].Our results are in concordance withDr. Krupali et al "A study of propofolauto-co-induction versus midazolam co-induction using priming principle bybispectral index analysis for ambulatory surgery" who in their study observed thatpostoperative RASS was high at any time interval with delayed recovery in Midazolamco-induction group[21].Our results correlate well with DeLucia and White et al "Effect of midazolam on induction and recovery characteristics of propofol" who comparedpropofol recovery profiles with the addition of 2 or 5 mg midazolam during induction of anaesthesia for ambulatory laparoscopies. The high-dose midazolam caused measurable but insignificant delay when compared with low dose midazolam[31].

CONCLUSION

Priming with midazolam co-induction or propofol auto-co-induction significantly reduces the induction dose requirement of propofol to maintain bispectral index between 45-50 in BIS guided anaesthesia.

Pre-dosing with midazolam co-induction is more effective than pre-dosing with propofol auto-co-induction in requirement of induction dose of propofol with advantage of cardiovascular stability but delayed recovery and discharge to home due to sedation in day care surgeries.

By using priming principle and BIS guided anaesthesia we can discharge the patients early in propofol auto-co-induction group, while it is delayed in propofol-midazolam group.

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