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ORIGINAL ARTICLE

Propofol or Midazolam for Sedation and Early Extubation Following Coronary Artery Bypass Graft Surgery

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ABSTRACT

Objective: To evaluate the efficacy of midazolam and propofol for postoperative sedation and early extubation following cardiac surgery.

Methods: This randomized control trial was conducted at the Cardiac Surgery Department of the Choudhary Pervaiz Elahi Institute of Cardiology from February 2019 to February 2020. A total of 60 American Society of Anesthesiologists (ASA) III patients planned to undergo coronary artery bypass graft surgery were included. After shifting into intensive care unit (ICU), patients were divided in two groups by lottery method and study drugs propofol and midazolam were started. Both infusions were terminated after four hours and patients were assessed for postoperative sedation and extubation. Hemodynamic parameters, arterial blood gases and respiratory functions were assessed and recorded.

Results: The mean time to awakening, time to extubation in midazolam group was 94.11±4.36 minutes, 94.47±6.11 minutes respectively and in propofol group it was 96.58±4.31 minutes, 91.91±3.94 minutes respectively. Difference was statistically significant.

Conclusion: Results of our study reveal that there was no difference in both drugs regarding sedation and extubation time, both drugs are safe, effective and useful in patients of coronary artery bypass graft surgery.

Keywords: Coronary artery bypass graft, Midazolam, Propofol, Extubation, Sedation.

INTRODUCTION

Propofol is an intra lipid and alkali phenol chemically it is unrelated to sedative agents or anaesthetic. It is an intravenous general anaesthetic that can be used for deep sedation in lower doses.[1] Propofol is formulated as emulsion with glycerol, soyabean oil or egg lecithin. Emulsion is formulated as one percent (10mg/ml) to make it antibacterial agent disodium acetate can be mixed.[2,3] Anaesthetic effect of propofol ranges from hyponosis to deep sedation but these effects are dose dependent. Propofol have many unique properties like rapid oneset of action, high clearance rate,[4] short duration of action, minimum drug accumulation property and lack of active metabolites, all these properties make propofol as an ideal anaesthetic.[5]

Midazolam is a banzodiazepen and most of its properties are similar to diazepam. Chemically midazolam is 8-chloro-5-1-methyl-4H-immidazobanzodiazepen meliate.[5-7] Midazolam is a powerful amnesic anticonvulsant anxiolatic hyponotic sedative and skeletal muscle relaxant. It has a very short half-life but a fast acting benzodiazepine.[8] It is a colourless crystal and it's each millimeter has 1.0 or 5.0mg midazolam with pH of 3.3 buffered. The acidic pH of midazolam is necessary to save the benzodiazepene ring when midazolam injected acidic environment of benzodiazepene close the ring and provide the chemical structure which is necessary for clinical efficacy of drug.[9-11]

The "Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients" in the ICU, known as PADIS guidelines, state that light sedation in adult ICU patients is associated with a decreased extubation time and eventually reduced rate of tracheostomy done in these patients.[12,13] These guidelines recommend that non-benzodiazepine drugs should be used in combination with analgesic drugs.[11]

Keeping in mind the major reason for ICU admissions, there are two groups of patients that need to be emphasized. These two groups are treated separately in the PADIS guidelines. The first population group are the patients that underwent elective cardiac surgery and will routinely be intubated for maximum 24 hours. The second group is made up of population that comprises of all the medical and surgical patients that need ventilation greater than 24 hours. According to the PADIS guidelines benzodiazepines drugs are not advisable, as a first line drug, to be used in both groups. This study was planned to evaluate the efficacy of midazolam and propofol for postoperative sedation and early extubation following cardiac surgery.

METHODS

The study was conducted in Cardiac Surgery Department of the Choudhary Pervaiz Elahi Institute of Cardiology in one year duration of February 2019 to February 2020. Study was started after approval from the Institution's Department of Academic Affairs (Letter#07, Dated: 01-01-2020). Written informed consent was obtained from the patients. Patients of age from 20 to 40 years, ASA III, either gender, patients who required coronary artery bypass graft surgery were included in the study. Patients with history of any psychiatric disease, use of antidepressant, alcohol abusers, obese, pregnant women were excluded from the study. Patients were taken NPO for minimum 6 hours and shifted to the operation theater where they were connected with ECG monitor, pulse oximeter, invasive blood pressure monitoring, monitoring of respiratory rate and oxygen saturation. This study was a double blind randomized controlled trial in which one group was given propofol at induction dose of 0.5mg/kg and after that maintenance dose was given 50mg/kg/min. Other group was given midazolam in a single dose 75mg/kg.

Patients were given oral bromazepam 3mg 60-90 minutes before surgery as premedication. After reaching operation theater, IV midazolam 2-5mg and fentanyl 25-50 Ug was given for facilitation of arterial and venous lines under local anesthesia. The agent used for the induction of anesthesia was propofol at a dose of 1-2mg/kg-1 and fentanyl 5 Ug.kg-1. In order to aid the tracheal intubation, atracurium 0.5 mg kg-1 was administered. Maintenance of anesthesia was done by continuous infusion of fentanyl in a dose of 1-2 mg.kg-1 .h-1 and isoflurane in oxygen/air at a concentration of 0.5-1.0%. Central venous line was placed under general anesthesia.

The monitoring of all the patients was done with ECG, pulse oximetry, direct arterial BP, urinary output and capnography during the surgery. The temperature was determined by the use of nasopharyngeal probe. The CPB (Cardiopulmonary Bypass) was established by using a membrane oxygenator and roller pump having arterial line filter. Antegrade cold crystalloid cardioplegic agent was given to every patient intermittently.

Immediately after shifting in ICU study drugs, propofol and midazolam was given and to remove bias two fluids started at

same rate prepared by pharmacist. Patients of propofol group received infusion of propofol one side and normal saline as placebo on other iv line, in midazolam group patients were given midazolam infusion and intralipid infusion as placebo. Propofol infusion was started at 10µg/kg/mim and midazolam was started at 0.25 mg/kg/min. Morphine at rate of 0.02 mg/kg/min was started for analgesia after shifting in ICU. Level of sedation was assessed by same researcher throughout study. After assessment of adequate sedation infusions were stopped and patients were weaned off from ventilator support.

Mechanical ventilation was e weaned off by assessing following criteria: Bleeding less than 100 ml/hr, body temperature more than 36 ^{0}C, adequate pain control, fully oriented and systolic blood pressure less than 140 mmHg. Time to extubation (from end of infusion), time to awakening (from end of surgery), time spent at each level of sedation, incidences of nausea, number of adjustments required to maintain sedation, morphine dose, vomiting and shivering were recorded on predesigned proforma. Respiratory function and arterial blood gases were recorded before and after extubation.

SPSS version 23 was used for data analysis, mean and SD were calculated for numerical variables like age, duration of surgery, CPB time and discharge time. Frequency and percentages were calculated qualitative data like gender, incidence of shivering and incidence of vomiting. Tests of significance (t-test and chi square tests) were applied to see association among variables. P value ≤ 0.05 was considered as significant.

RESULTS

In a total of 60 patients, there were 48 (80.0%) male and 12 (20.0%) female. Mean age, weight and height of the midazolam was 46.63±5.71 years, 64.86±3.44 kg and 165.41±4.34 cm, respectively. The mean duration of operation and duration of CPB was 185.13±4.62 minutes and 75.45±2.58 minutes, respectively. The mean discharge time ICU and hospital was 7.81±0.93 days and 5.61±2.64 days, respectively. There were n=27 (90.0%) males and n=3 (10.0%) females. While, the mean age, weight and height of the propofol was 44.83±4.44 years, 64.46±4.24 kg and 165.96±5.32 cm, respectively. The mean duration of operation and duration of CPB was 186.91±4.98 minutes and 65.21±1.24 minutes, respectively. The mean discharge time ICU and hospital was 7.93±1.73 days and 7.85±1.32 days, respectively. There were n=21 (70.0%) males and n=9 (30.0%) females. Types of operation are presented in Table-I. The differences were statistically insignificant except discharge time hospital (p<0.001). (Table-I).

Table-1: Demographics and intraoperative characteristics of the patients

Variable	Midazolam (n=30)	Propofol (n=30)	P-value
Age (years)	46.63±5.71	44.83±4.44	0.178
Gender			
Male	27 (90.0%)	21 (70.0%)	0.063
Female	3 (10.0%)	9 (30.0%)	
Weight in kg	64.86±3.44	64.46±4.24	0.690
Height in cm	165.41±4.34	165.96±5.32	0.832
Duration of operation (min)	185.13±4.62	186.91±4.98	0.874
Duration ofCPB (min)	75.45±2.58	65.21±1.24	0.321
Discharge time			
ICU (days)	7.81±0.93	7.93±1.73	0.627
Hospital (days)	5.61±2.64	7.85±1.32	<0.001

The mean rate of administration, total amount of study drug, intraoperative sufentanil and postoperative morphine of midazolam group was 0.23±0.035 µg.kg-^{t}.min^1, 4.52±1.15 mg, 0.98±0.042 µg.kg^{-1}.hr^{1}and 4.82±1.82 mg, respectively. While, the mean rate of administration, total amount of study drug, intraoperative sufentanil and postoperative morphine of propofol group was 11.16±2.32 µg.kg-^{t}.min^1, 185.56±2.51 mg, 1.11±0.025 µg.kg^{-1}.hr^{1}and 3.25±0.99 mg, respectively. The differences in between study groups were statistically significant in terms of drugs administration (p<0.001) as shown in Table-II.

Table-2: Drug administration of the patients

Variable	Midazolam (n=30)	Propofol (n=30)	P-value
Rate of administration	0.23±0.035	11.16±2.32	<0.001
Total amount of study drug	4.52±1.15	185.56±2.51	<0.001
Intraoperative sufentanil	0.98±0.042	1.11±0.025	<0.001
Postoperative morphine	4.82±1.82	8.25±0.99	<0.001

The mean time to awakening, time to extubation, FVC preoperative, FEV_1 preoperative, FVC_1 postoperative, FEV $_1$ postoperative, P_aO_2 during CPAP, P_aO_2 after extubation, P_aCO_2 during CPAP and P_aCO_2 after extubation of midazolam group was 94.11±4.36 minutes, 94.47±6.11 minutes, 3.69±1.07 (L), 2.81±0.93 (L), 1.07±0.89 (L), 1.38±0.29 (L), 134.77±5.04mmHg, 139.33±8.67mmHg, 49.56±6.15mmHg and 47.34±4.53mmHg, respectively. While, the mean time to awakening, time to extubation, FVC preoperative, FEV_1 preoperative, FVC_1 postoperative, FEV $_1$ postoperative, P_aO_2 during CPAP, P_aO_2 after extubation, P_aCO_2 during CPAP and P_aCO_2 after extubation of propofol group was 96.58±4.31 minutes, 91.91±3.94 minutes, 3.43±0.87 (L), 3.06±0.76 (L), 1.13±0.97 (L), 1.28±0.35 (L), 133.91±5.94mmHg, 139.22±6.24mmHg, 50.57±5.77mmHg and 48.62±5.65mmHg, respectively. The differences were statistically insignificant (Table-III).

Table-3: Recovery characteristics and respiratory data of the patients

Variable	Midazolam (n=30)	Propofol (n=30)	P-value
Time to awakening	94.11±4.36	96.58±4.31	0.061
Time to extubation	94.47±6.11	91.91±3.94	0.059
FVC preoperative	3.69±1.07	3.43±0.87	0.302
FEV_1 preoperative	2.81±0.93	3.06±0.76	0.254
FVC_1 postoperative	1.07±0.89	1.13±0.97	0.806
FEV $_1$ postoperative	1.38±0.29	1.28±0.35	0.210
P_aO_2 during CPAP	134.77±5.04	133.91±5.94	0.547
P_aO_2 after extubation	139.33±8.67	139.22±6.24	0.954
P_aCO_2 during CPAP	49.56±6.15	50.57±5.77	0.994
P_aCO_2 after extubation	47.34±4.53	48.62±5.65	0.839

The mean CK-MB value (U.L $^{-1}$) at 8 hours, 16 and 24 hours, blood loss at first 3 hours and total of midazolam group was 34.53±11.07, 22.93±6.11, 17.81±4.72, 377.71±9.02ml and 877.31±11.12 ml, respectively. Incidence of shivering and incidence of nausea was noted as n=6 (20%) and n=9 (30%), respectively. While, the mean CK-MB value (U.L $^{-1}$) at 8 hours, 16 and 24 hours, blood loss at first 3 hours and total of propofol group was 35.61±8.38, 22.65±6.11, 18.25±6.32, 382.25±9.65ml and 881.25±10.24, respectively. Incidence of shivering and incidence of nausea was noted as n=8 (26.7%) and n=16 (53.3%), respectively. The differences were statistically insignificant (Table-IV).

Table-4: Postoperative events in the first 24 hours of the patients

Variable	Midazolam (n=30)	Propofol (n=30)	P-value
CK-MB value (U.L $^{-1}$)			
At 8 hours	34.53±11.07	35.61±8.38	0.676
16 hours	22.93±6.11	22.65±6.11	0.850
24 hours	17.81±4.72	18.25±6.32	0.644
Blood loss			
At first 3 hours	377.71±9.02	382.25±9.65	0.061
Total	877.31±11.12	881.25±10.24	0.179
Incidence of shivering	6 (20.0%)	8 (26.7%)	0.542
Incidence of nausea	9 (30.0%)	16 (53.3%)	0.067

DISCUSSION

ICU care for post-operative cardiac surgery patients is expensive.[14,15] After surgery 90% of ventricle function is recovered within four hours.[16] With appropriate analgesics, sedation, and avoidance from respiratory depressants extubation time can be reduced and trachea can be free. It is a desire of surgeon and

anesthetist to extubate the patient earlier, but a controlled sedation is necessary for this purpose.[17]

The results of our study are comparable to other studies reported in literature. In a randomized control trial conducted by Aghdaii and colleuges,[18] Fifty patients who were admitted in the ICU after coronary artery bypass grafting were was randomized into two groups. One group received sedation with midazolam and the other group received sedation with propofol infusions. They employed ramsay sedation score to assess the level of sedation. The found the total dose of additional fentanyl required for sedation was more in the midazolam group as compared to the propofol group (p= 0.0039). Moreover, the mean extubation time was 102 27mins in propofol group and it was 245 42 minutes in the midazolam group, this difference was statistically significant (p<0.05). This result is in contrast with the results of this study as we observed no statistically significant difference in the mean extubation time among the study groups. (p=0.05). The discharge time from ICU in the study conducted by Aghadii and colleagues was not statistically significant among the study groups, the results of discharge time from ICU were similar to these results.[18]

In a study conducted by Higgins et al.[19] similar infusions (i.e. midazolam and propofol) were assessed for 12 hours and reported that there was no difference in extubation time and ICU discharge. His conclusion is different from other studies where high doses of opioids were used and sedative infusions were used in intraoperative period.

Prolonged sedation was also reported in midazolam patients because of its accumulation in ICU patients after CABG. In contrast early decline was reported at propofol termination after prolonged infusion. Snellen et al.[20] conducted a similar study and reported early extubation in propofol patients, this study is contrast with our findings. McMurray et al.[21] conducted a similar study and reported same findings in favor of propofol group. Extubation time was reported low in propofol group in comparison to midazolam. In our study we didn't find any difference between both groups. However, the total dosage of morphine used was more in propofol group as compared to the midazolam group.

Limitations: There are some limitations to this study i.e. it has a small sample size and it's a single center study. Moreover, depth of sedation is not assessed in this study.

CONCLUSION

Results of our study reveal that there was no difference in both drugs regarding sedation and extubation time. Both drugs are safe, effective, and useful in patients of coronary artery bypass graft surgery. More multi-center studies with adequate sample size are necessary to validate the results of this study.

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