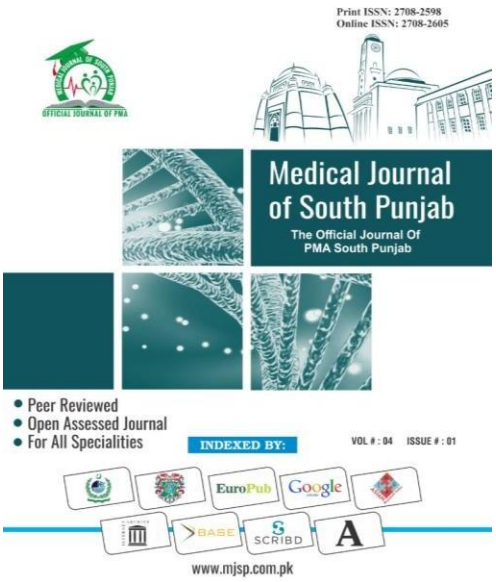
ISSN (E): 2708-2601
ISSN (P): 2708-2598

Medical Journal of South Punjab
Article DOI: 10.61581/MJSP.VOL04/01/06
Volume 4, Issue 1, 2023



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Publication History

Received: Jan 05, 2023 Revised: Feb 01, 2023
Published: June 03, 2023 Accepted: May 13, 2023

Authors and Affiliation:

Shahid Hussain[1*], Hira Asad[2], Hamid Mehmood[3], Imran Ali[4], Imran Hafeez[5], Rashid Hussain[6]
[1]Murshid Hospital & Health Care Center, Pakistan
[2]Memon Medical Institute Hospital, Pakistan
[3]Dow University Hospital Ojha
[4]Sindh Employees Social Security Hospital Karachi, Pakistan
[5]King Abdullah Medical City, Makkah, Saudi Arabia
[6]NICVD Hospital, Karachi, Pakistan
Corresponding Author Email:
[*]dr.hira@live.com

Conflict of Interest:

Author(s) declared no conflict of interest.

Acknowledgment:

No Funding received.

Citation: Hussain S, Asad H, Mehmood H, Ali I, Hafeez I, Hussain R. Propofol or midazolam for sedation or Early Extubation following coronary artery bypass graft surgery. Medical Journal of South Punjab. 2023 June 3; 4(1):51-59.

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An official publication of
Medteach Private Limited, Multan, Pakistan.
Email: farman@mjsp.com.pk, Website: https://mjsp.com.pk/index.php/mjsp

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Volume 4, Issue 1, 2023; pp: 51-59
Original Article

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

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[2]Memon Medical Institute Hospital, Pakistan
[3]Dow University Hospital Ojha
[4]Sindh Employees Social Security Hospital Karachi, Pakistan
[5]King Abdullah Medical City, Makkah, Saudi Arabia
[6]NICVD Hospital, Karachi, Pakistan
[*]Corresponding Author Email: [*]dr.hira@live.com

ABSTRACT

Objective: *Study aimed to evaluate the efficacy of Midazolam and Propofol for postoperative sedation and early extubation following cardiac surgery.*

Methods: *Randomized control trial was conducted at cardiac anesthesia department of National Institute of Cardiovascular Diseases, Karachi Pakistan in one-year duration of 1st February 2018 to 30th January 2019. Patients with ASA 3 who was selected for coronary artery bypass graft surgery. After shifting in 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 extubation. Hemodynamic parameters arterial blood gases and respiratory function was 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 bypasses graft, Midazolam, Propofol, Extubation, Sedation

1. INTRODUCTION

Propofol is an intra lipid and alkali phenol chemically it is unrelated to sedative agents or anesthetic. It is an intravenous general anesthetic can be used for deep sedation in lower doses[1]. Propofol formulated as emulsion with glycerol, soybean oil or egg lecithin. Emulsion is formulated as one percent (10mg/ml) to make it antibacterial agent disodium acetate can be mixed[2,3]. Anesthetic effect of propofol ranges from hypnosis to deep sedation but these effects are dose dependent. Propofol have many unique properties like rapid onset 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 benzodiazepine. 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, anxiolytic, hypnotic, sedative and skeletal muscle relaxant. It has very short half-life but a fast acting benzodiazepene[8]. It is a colorless crystal. 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 benzodiazepine ring when midazolam injected acidic environment of benzodiazepine close the ring and provide the chemical structure which is necessary for clinical efficacy of drug[9,10].

2. METHODOLOGY

The study was conducted in cardiac anesthesia department of National Institute of Cardiovascular Diseases (NICVD), Karachi Pakistan in one-year duration of 1st February 2018 to 30th January 2019. Study was started after approval from the hospital ethical board. Written informed consent was obtained from the patients. Patients of age from 40 to70 years, ASA status 3 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 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 0.03mg/kg midazolam and morphine 0.015mg/kg

90&30min respectively 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 and patients of midazolam group were given midazolam infusion. Propofol infusion was started at 10µg/kg/mim and midazolam was started at 0.25 mg/kg/min. Toradol 30mg I/V Stat were given 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 can be weaned off by assessing following criteria: Bleeding less than 100 ml/hr, body temperature more than $36C^0$, 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 performa. Respiratory function and arterial blood gases were recorded before and after extubation.
SPSS version 23 was used for data analysis, mean and SD was 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.

3. RESULTS

Sixty patients were included in this study, both genders. The patients were equally divided into two groups as Midazolam n=30 (50%) and n=30 (50%) Propofol. The 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 was n=27 (90%) males and n=3 (10%) 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 was n=21 (70%) males and n=9 (30%) females. Types of operation were presented in table I. The differences were statistically insignificant except discharge time hospital (p=0.000). (Table. I).

The mean rate of administration & total amount of intraoperative fentanyl and postoperative toradol of midazolam group was 0.23±0.035 $\mu g.kg^{-t}.min^{1}$, 4.52±1.15 mg, 0.98±0.042 $\mu g.kg^{-1}.hr^{1}$and 4.82±1.82 mg, respectively. While, the mean rate of administration, total amount of study drug, intraoperative fentanyl and postoperative toradol of propofol group was 11.16±2.32 $\mu g.kg^{-t}.min^{1}$, 185.56±2.51 mg, 1.11±0.025 $\mu g.kg^{-1}.hr^{1}$and 3.25±0.99 mg, respectively. The differences were statistically significant. (Table. II).

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-I: **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	n=27 (90%)	n=21 (70%)	0.063
Female	n=3 (10%)	n=9 (30%)	
Weight	64.86±3.44	64.46±4.24	0.690
Height	165.41±4.34	165.96±5.32	0.832
Type of operation			
CABG	n=16 (53.3%)	n=22 (73.3%)	0.108
Valvular	n=10 (33.3%)	n=11 (36.7%)	0.787
ASD	n=0 (0%)	n=2 (6%)	0.654
Duration of operation (min)	185.13±4.62	186.91±4.98	0.874
Duration of CPB (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	0.000

Source: Author's Own Calculation

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-II: 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	0.000
Total amount of study drug	4.52±1.15	185.56±2.51	0.000
Intraoperative fentanyl	0.98±0.042	1.11±0.025	0.000
Postoperative toradol	4.82±1.82	8.25±0.99	0.000

Table-III: 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	3.69±1.07	3.43±0.87	0.30

preoperative			2
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

Table-IV: 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	n=6 (20%)	n=8 (26.7%)	0.542
Incidence of nausea	n=9 (30%)	n=16 (53.3%)	0.067

4. DISCUSSION

Most expensive and time in hospital is ICU care in cardiac surgery patients. After surgery 90% of ventricle function recovered within four hours[11]. 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 extubated patient earlier but a controlled sedation is necessary for this purpose[12].

In a study conducted by Higgins et al[13] similar infusions were assessed for 12 hours and reported that there was not any 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. Almassi et al[14] conducted a study on patients regarding sedation of endoscopic procedures and reported more effective recovery and from sedation with use of combination of midazolam and Propofol.

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[15] conducted a similar study and reported early extubation in propofol patients, this study is contrast with our findings. Walder et al[16] conducted a study on comparison of midazolam plus

Propofol and Propofol alone in terms of sedation and early extubation time and reported that combination of both drugs reduced the mechanical ventilation or extubation time as compare to Propofol alone.

In our study we observed no significant difference in awakening time but extubation time is much lower in Propofol group. McMurray et al[17] 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. In another study by Searle et al[18] it was observed that there was no difference between two groups regarding sedation time and time taken for extubation.

Carrasco et al[19] compared different doses of Midazolam in sedation of patients and reported that Midazolam 2 mg/h is more effective in appropriate sedation. In our study we used 1 mg/h Midazolam and results were same as in Carrasco study. In another study Magarey et al[20] conducted a review on propofol and midazolam and reported that propofol have early sedation and recovery time as compare to midazolam in cardiac surgery patients.

5. 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.

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