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Frequency of Delirium Associated with Dexmedetomidine and Propofol in Post CABG Patients: A Comparative Study

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ABSTRACT

Objective: To find out the frequency of delirium associated with peri-operative use of dexmetedomidine and propofol in post CABG patients.

Study Design: Comparative Cross-sectional study.

Place and Duration of Study: Adult Intensive Care unit, Department of Cardiac Anesthesiology and Intensive Care, Armed Force Institute of Cardiology, Rawalpindi Pakistan from Feb to Jun 2022.

Methodology: All post CABG patients who have undergone elective surgery were included through non-probability consecutive sampling technique. All the delirious patients amongst them were subjected to a modified version of ICU-CAM to establish post-operative delirium (POD) caused by either dexmedetomidine or propofol. POD in both the category of patients was compared.

Results: A total of 179 CABG patients were included in our study. 140(78.2%) of the patients were subjected to the use of dexmedetomidine throughout their surgery while 39(21.8%) of the patients were given propofol. After subjecting the patients to our exclusion criteria which aimed to eliminate the confounding causes of POD in post-CABG patients, only 30(16.8%) had delirium while 149(83.2%) didn't develop delirium (*p*-value=0.003). Majority of the delirious patients were given dexmedetomidine (n=29; 20.77%) in the operation theatre while only a fraction (n=1; 2.58%) were given propofol. Average duration of ICU stay in our study population was 5 days. 15(8.4%) cases out of our total study population underwent re-intubation and re-ventilation because of low cardiac output or respiratory distress.

Conclusion: Dexmedetomidine could possibly be associated with POD in patients undergoing cardiac surgery. Propofol on the other hand is considerably safe in this regard and doesn't cause POD.

Keywords: Cardiac surgery, Dexmedetomidine, Post-operative delirium.

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INTRODUCTION

Practice of Anesthesia includes using induction followed by maintenance anesthesia drug in order to reduce intra-operative awareness and therefore the aim is to increase the depth of Anesthesia.[1] Propofol and Dexmedetomidine are most commonly used for this purpose especially in cardiac surgery. Dexmedetomidine is an imidazole derivative and active d-isomer of medetomidine with basic actions being analgesic and sedative with some degree of anxiolytic properties. It essentially works by binding to the pre-synaptic alpha adrenoceptors inhibiting the release of adrenaline and thus causing depression of sympathetic response at post synaptic level in the brain and spinal cord.[2] Unlike most of the clinically used anesthetia drugs, dexmedetomidine brings about a sedative-hypnotic effect via an action on a single type of receptors and also has an analgesic effect and an autonomic blockade that is beneficial in cardiac risk situations. However, bradycardia and hypotension are its most commonly encountered adverse effects.[3] Propofol works by inhibiting the dissociation of GABA from GABA receptors potentiating its effects which are predominantly inhibitory on the synaptic activity of neurons.[4] Post-operative delirium (POD) is a common neurological complication after cardiac surgery. It usually peaks between post-operative day one to three in the vulnerable patient population,[5,6] Old age, diabetes, history of stroke, long term use of alcohol consumption and having extra cardiac vascular disease puts a patient at risk of developing POD after undergoing CABG,[7] In addition, many drugs used in the practice of cardiac anesthesia might pre-dispose the patient to POD. While Dexmedetomidine is largely documented to be of great benefit to treat psychosis in post-operative CABG patients,[8] our study aimed to find if it was actually causing psychosis in such patients or not.

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POD manifests as either irritability, confusion and tendency to self-harm or drowsy unresponsive patient. Whatever the spectrum of presentation, patient's cognitive functions decline and differ from his baseline cognition and mental functions.

Post-operative delirium (POD) causes enhanced morbidity in post CABG patients and results in prolonged ICU stay especially in the elderly, thus putting a strain on the healthcare resources.[9,10]

Existing literature shows conflicting results regarding the use of dexmedetomidine and its effects on post-operative delirium. While some researchers have concluded it to be effective in reducing post-operative delirium, (POD) a meta analysis done by Society of Thoracic Surgeons from their Adult Cardiac Surgery Database has reported that use of dexmetedomidine peri-operatively increases not only the frequency of POD but also post-operative re-intubation and re-ventilation and overall morbidity and mortality thereby.[11]

No such pre-existing study has been conducted so far on our subset of the population so we have designed this particular study to find out the frequency of dexmetedomidine and propofol associated delirium in post CABG patients and the impact it has on over all duration of ICU stay of such patients.

METHODOLOGY

After taking approval of the Institutional Review Board, Armed Force Institute of Cardiology, Rawalpindi Pakistan the study was initiated. This is a comparative cross-sectional study set up in the Adult ITC, Department of Cardiac Anesthesiology and Intensive Care, AFIC Rawalpindi from February to June, 2022 with a sample size of 178.

Sample Size: The sample size (n=178) was calculated using WHO sample size calculator and the incidence of delirium after cardiac surgery was taken as 13.3% as per a study set up in Vilnius University, Clinic of Anesthesiology and Intensive Care, Faculty of Medicine.[12]

Inclusion Criteria: All the elective CABG cases subjected to the use of dexmedetomidine or propofol in the operation theatre for the duration of surgery were included in the study aged 35 to 85 years. Dose of these drugs was titrated according to the sedation level desired by the anesthesiologist. Dexmedetomidine was used in doses of 0.2-0.5mcg per kg body weight / hour and Propofol was used in dose of 1-2.5 mg per kg body weight/ hour. Any patient found to be delirious post operatively while staying in the ICU was subjected to a modified version of ICU-CAM,[13] including the RAAS.[14] All the causes of delirium commonly found in cardiac patients which could serve as confounding factors were essentially eliminated through our exclusion criteria.

Exclusion Criteria: Emergency CABG cases; H/O Chronic Kidney Disease /Acute Kidney Failure (Raised Creatinine levels >2mg/dL), H/O Chronic Liver Disease -History of Hepatitis B or C, Low Cardiac Output (Central Venous Oxygen saturation of < 60%), Pain of severity 8/10 or more not relieved by Intravenous medication/opioid patch, Any sleep/Wake Disturbances, Prolonged TBT > 150 mins or more were excluded.

Sampling technique was non-probability consecutive sampling by taking formal approval from institutinal IERB (Ltr# 9/2/R&D/2022/185). Data confidentiality was maintained. After data collection, it was analyzed on SPSS-22 and Microsoft Excel. Descriptive stats were applied to measure Mean±SD deviation, (SD) frequency and percentages. Chi Square test and T-test was applied by considering *p*-value <0.05

RESULTS

179 patients that underwent elective CABG were included in our study. 63(35.2%) were females while 116 (65%) were males. Mean age of the study participants was 60.82±7.354 years. The predominantly found comorbidities were diabetes mellitus, hypertension and COPD. Figure shows the frequencies of these comorbidities amongst our study population. 125 (69.8%) of the patients were non-smokers while 54 (30.2%) were smokers. 29(16.25%) patients had a history of stroke as well. Average duration of ICU stay of our study population was 5 days. 15(8.4%) cases amongst our study population underwent re-intubation and ventilation. The cause of this was mainly low cardiac output and respiratory distress.

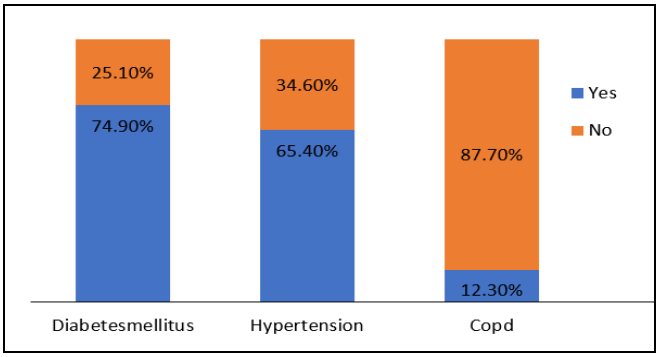

Figure: Common Comorbities in Patients

140(78.2%) of the patients were subjected to the use of dexmedetomidine peri-operatively while 39 (21.8%) of the patients were given propofol in the operation theatre. After subjecting the patients to our exclusion criteria, only 30(16.8%) had delirium while 149(83.2%) didn't suffer from this complication, *p*-value of 0.03 was computed which was considered significant. Among the 30 patients who developed POD, 29 cases were given dexmedetomidine and while only 1 of the delirious patients was given propofol.

13(43.3%) of the total delirious patients were females while 17(56.6%) were males. Table-I shows a comparison of the frequency of delirium by the use of the two drugs under consideration. Most cases of POD were see on post-operative day three i.e.,

Table-I: Drug related frequency of Delirium in Study Population

	Dexmedetomidine	Propofol
Total Patients Receiving the Drug	140(78.20%)	39(21.8%)
Incidence of Delirium Caused by that Drug (POD)	29(20.71%)	1(2.56%)

7 cases (3.9%) out of all the delirious cases were largely agitated, confused and managed for delirium on day 3 after their surgery. An interesting finding with regards to the comorbid conditions is that 28/30 (93.3%) patients developing delirium were diabetics, while 23/30 (76.6%) were hypertensive patients, reflecting the chronic diseases effecting the post-operative recovery and complications of patients. t-test of significance was applied to obtain the *p*-value. Table-II shows a detailed comparison of various variables amongst our two study groups of patients along with *p*-value.

Table-II: Comparison of Variables Among Study Groups

Variable		Grouping		*p*-value
		Dexmedatomidine (n=140)	Propofol (n=39)	
Gender	Female	46 (32.85%)	17 (43.58%)	0.147
	Male	94 (67.14%)	22 (56.41%)	
Diabetes				
Yes		108 (77.14%)	26 (66.6%)	0.131
Hypertension				
Yes		96 (68.57%)	21 (53.84%)	0.066
COPD/Asthma				
Yes		11 (7.85%)	11 (28.20%)	0.002
Smoker				
Yes		39 (27.85%)	15 (38.46%)	0.141
Perioperative Dexmedatomidine				
Yes		140 (100%)	-	-
Perioperative Propofol				
Yes		-	39 (100%)	-
POD				
Yes		29 (20.71%)	1 (2.56%)	0.003
Re-intubation				
Yes		12 (8.57%)	3 (7.69%)	0.580

There was statistically insignificant association between different variables (*p*-value>0.05) in group-C & group-D except COPD and POD (*p*=0.002 and *p*=0.003 respectively).

DISCUSSION

Our study aimed at finding the frequency of delirium in post CABG patients in relation to the peri-operative use of dexmedetomidine and propofol. The patients in our study were subjected to a modified version of ICU-CAM and then they were studied for development of delirium during their stay in ICU.

To pinpoint a single cause of POD in post CABG patients is very perplexing and cumbersome. It is multifactorial and regardless of the cause, leads to increased morbidity and mortality. Brown *et al*. reports overall frequency of POD to be between 26-52% in post CABG patients while our study which focuses on dexmedetomidine and propofol associated delirium only reports a lower incidence of 16.8% excluding the patients with the other causes of POD.[15]

Dexmedetomidine is widely used in the setting of Cardiac ICUs. Our study found that 29(20.71%) of the patients receiving this drug developed POD. Many researches worldwide had found dexmedetomidine as a cause of POD in post CABG patients. Paul *et al*. did a meta analysis on the same subject and stated that POD is a possible neurological side effect of dexmedetomidine and increases rates of re-intubation and re-ventilation in post CABG patients,[11] as reinforced by our study findings. Li X *et al*. in a randomized controlled trial and Oh S-T *et al*. both found that dexmedetomidine doesn't decrease the overall incidence of POD.[6,16] This also is similar to the results of our study where a statistically significant cause of delirium (*p*-value 0.03) was the peri-operative use of dexmedetomidine and propofol.

Furthermore, a study setup in the department of Anesthesiology, West China Hospital, Sichuan University carried out a comparative analysis in patients undergoing thoracic surgery. They compared the effect of placebo and dexmedetomidine over POD in early post-operative period. The two groups of patients had nearly comparable rates of POD. 36.54% in dexmedetomidine group and 32.00% in placebo group. Our study although very simple in design had similar findings that dexmedetomidine had caused delirium in 20. 71% people and is not a cure for POD.[17]

Several studies however including a metaanalysis of Randomized Control Trials carried out by Li *et al*.

and Xiong *et al*. had opposite findings and the result of pooled studies was found to be in favor of dexmedetomidine in reducing POD in cardiac surgery patients.[18,19] Thus the literature is largely conflicted.

The consensus on propofol is that it is a sedative drug with particular benefits in treating POD in post CABG patients. In our study, only one patient receiving propofol developed delirium thereby reaffirming its efficacy as a good sedative drug reducing the overall incidence of POD like the findings of Ishii *et al*.[20]

LIMITATIONS OF STUDY

The limitation of our study was the uniformity of sample size. Unequal number of patients were present in both the groups because of the difference of hemodynamic status and cardiovascular disease of each patient, based on which the anesthesiologist would decide the need for either dexmedetomidine or propofol in real time. Limited sample size and duration were also contributing factors.

CONCLUSION

Post-operative delirium is a common neurological complication in post-CABG patients. It increases the overall morbidity and duration of ICU stay. There is an increased need for re-intubation and re-ventilation in delirious patients. Dexmedetomidine could possibly be associated with POD in post- CABG patients. Propofol on the other hand is considerably safe in this regard and can be used an effective sedative drug for the treatment of POD.

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Conflict of Interest: None.

Auhtor's Contribution

Following authors have made substantial contributions to the manuscript as under:

NA: Concept, Literature review, manuscript writing
SMHK: Concept, intellectual contribution, critical review
AS: Manuscript writing, data analysis, review
MUS: Data entry, correction, editing
RJ: Manuscript writing, Data analysis, Data collection, Entry,
MAK: Proof reading Intellectual contribution, critical review

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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